TO DETERMINE THE ROLE OF RERESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER

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Submitted By

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Dedicated

to

my Family,

friends

&

Teachers

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Dr. Nikhil Chauhan

ABBREVIATIONS

NMIBC	: Non-Muscle Invasive Bladder Cancer
PFS	: Progression-Free Survival
HR	: Hazard Ratio
TURBT	: Transurethral Resection of Bladder Tumor
CT	: Computed Tomography
MRI	: Magnetic Resonance Imaging
WLC	: White Light Cystoscopy
HAL-BLC	: Hexaminolevulinic Acid-Blue Light Cystoscopy
5-ALA	: 5-Aminolaevulinic Acid
CIS	: Carcinoma In Situ
TNM	: Tumor, Node, Metastasis
UICC	: Union for international Cancer Control
AJCC	: American Joint Committee on Cancer

ABSTRACT

INTRODUCTION: High-grade non-muscle invasive bladder cancer (NMIBC) poses a significant risk of recurrence and progression, necessitating effective management strategies. Re-TURBT, a second-look transurethral resection of bladder tumor, has emerged as a critical component in the treatment paradigm. This abstract reviews the current evidence and guidelines supporting the role of Re-TURBT in optimizing outcomes for patients with high-grade NMIBC.

AIM AND OBJECTIVE: To assess the role of second TUR in T1G3 bladder tumors and identify subgroups that may not require this procedure.

METHODS: This prospective study included 30 patients with T1G3 disease who underwent second TUR at Dayanand Medical College and Hospital, Ludhiana, Punjab, from October 2022 to February 2024. Variables like tumor size, multifocality, and characteristics were analyzed.

RESULTS: 63% of lesions were solitary, and 83% were large (>3cm). 56% of patients had residual disease or recurrence at second TUR, and 6.67% were upstaged. Patients with solitary lesions and small tumor size (<3cm) had lower rates of residual disease.

CONCLUSION: Patients with T1G3 tumors do not represent a homogeneous group. A second TUR is recommended to identify residual and invasive disease, our findings suggest that patients with solitary papillary lesions and small tumor size may not require this procedure, but for multiple tumor or larger tumor , re TURBT is necessary to restage the tumor in pursuit of providing most optimal treatment. .

KEYWORDS: re-TURBT, solitary lesion, multifocality, residual disease, high grade tumor, T1 bladder cancer

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INTRODUCTION

The ninth most prevalent cancer in the world and the 13th most frequent cause of death is bladder cancer (Nieder et al., 2005).[1] Men and Caucasians are more commonly affected than women and Asians. Male mortality rates are 2–10/100,000, whereas female death rates are 0.5–4, age-standardized (Kirkali et al., 2005). [2]Bladder cancer is classified into three histopathological categories (i) Transitional cell carcinoma: the commonest type, arising in the innermost layer of cells and classified into high and low grades (ii) Squamous cells are the source of squamous cell carcinoma (iii). Adenocarcinoma: Develops from the epithelium glandular.

Non-muscle invasive bladder Ca (NMIBC) is cancer that does not penetrate the muscularispropria, while muscle-invasive bladder cancer are cancer that have penetrated into muscle. High-risk non-muscle bladder cancer has a higher progression rate and recurrence. The transitional type of bladder cancer is most frequent (95%) followed by squamous cell cancer (5%) with the least common variant being adenocarcinoma (2%).
Treatment Options According to TNM

1) Stage 0
   a) Trans-urethral resection of bladder tumor (TURBT) followed by Intravesical BCG(Chemotherapy)
   b) Partial cystectomy

2) Stage I
   a) TURBT followed by Intravesical BCG/ Chemotherapy
   b) Partial cystectomy
   c) Radical cystectomy with neo-adjuvant chemotherapy

3) Stages II and III

a) Radical cystectomy
b) Radiotherapy with neo adjuvant chemotherapy
c) Partial cystectomy
d) Radical TURBT
e) Immunotherapy

4) Stage IV

a) Palliative radiotherapy with chemotherapy
f) Palliative radical cystectomy with palliative adjuvant chemotherapy/ Immunotherapy

NMIBC includes Stages 0 and I bladder cancer while Stages II, III, and IV are MIBC. TURBT eradicates all visualized growth in the bladder and biopsy is sent for histopathological examination. The quality of primary TURBT specimen is paramount and must include complete resection of tumor including the suspected tumor and the detrusor to find out muscle involvement which helps in decreasing the recurrence rate and progression (Herr et al., 2005).[3] The 'International Bladder Cancer Group' defines not only progression from non-muscle invasive to muscle-invasive but also a progression from CIS/Ta to T1 as disease upgrading (Lamm et al., 2014). [4]

In 70–85% of cases, bladder urothelial carcinoma is identified as a non-muscle invasive papillary tumor (Herr et al., 2006). [3] It is noteworthy that 10% of pTa tumors and 35% of pT1 tumors will develop to muscle invasive illness. Recurrence rates in this group range from 0 to 80%. Tumor size, multi-focality, stage, grade, and early recurrence have been shown to be correlated with the course of disease (Herr et al., 2006). [3]

TURBT is the first step in the treatment of Ta, T1, and CIS and removal of all visualized bladder growth, out of which half of T1 patients show

remaining growth and about 25% of cases result in upstaging after 2–6 weeks of primary TURBT in high-risk NMIBC patients, particularly in whom there was non-availability of muscle in the primary specimen (Divrik et al., 2010).[5] Factors influencing the result of primary TURBT include multifocal growth, huge tumor size, or involving whole bladder with no distinguished margin and too much vascular growth, leading to intraoperative heavy bleeding, technique, and experience of surgeon and skills of the pathologist. These subsequently lead to tumor underestimation in approximately 10–50% of cases with NMIBC after primary TURBT. The "gold-standard" for treating non-muscle invasive bladder ca is still TURBT combined with intra-vesical chemotherapy. However, initial TUR can not be sufficient enough to completely remove and stage the tumour, which increases tumour recurrence and progression risk. According to Herr et al. (2006), [3] individuals with high-grade non-muscle invasive bladder Ca (HG-NMIBC) may experience a 33–53% residual tumor incidence after initial TURBT. Furthermore, 10% of first resections are considered to be understaged. According to guidelines published by the 'European Association of Urology' (EAU) in 2003 and 2006, recurrence-free survival may be enhanced by early re-resection.

Regarding the role of recurrent transurethral resection (reTURBT) of bladder in non-muscle-invasive bladder cancer (NMIBC), however, there are still very poor clinical evidence available. According to international guidelines, if an incomplete initial TUR results in no detrusor muscle (DM) in the specimen, a second resection should be performed within 2-4 weeks of the first TUR, with the exception of low-grade (LG)/G1 Ta tumors, primary carcinoma in situ (CIS), and all T1 tumors (Babjuk et al., 2022). [6] The danger of understaging (up to 50% in previous series of patients with G3 T1 disease treated with upfront radical surgery) and the high risk of remaining disease after the initial resection, which varies from 17% to 71%, depending on the series, are the reasons for conducting reTUR.

Regarding reTUR's function, not all studies accord. When DM was present in the first TUR specimen, there was no benefit for reTUR, according to a recent large retrospective analysis of patients with G3 T1 illness treated with BCG (Gontero et al., 2016).[7] Therefore, it is debatable about whether patients with detrussor muscle (DM) in the TUR specimen (which is thought to be a proxy for high-quality TUR and precise staging) can avoid having a second TUR (Holmäng et al., 2013).[8] Additionally, attempts are made to look into predictors of residual disease and/or upstaging in order to spare certain patients from reTUR, however the majority of the results have been disappointing (Culpan et al., 2022). [9] There is only one RCT to date that compares reTUR versus no reTUR in patients undergoing intravesicalmitomycin C instillations.

A new study investigating the clinical value and safety of reTURBT in patients stratified by clinical indications is thus essential to fill the current evidence gap in this field. Our study has aimed to explore the role of re-resection in high grade non-muscle invasive bladder cancer.

Rationale of the Study

TURBT serves as a critical procedure for initial treatment and diagnosis of bladder carcinoma. It aims to achieve complete resection of visible tumors, enabling accurate histological staging and grading. This distinction between non-muscle invasive and muscle-invasive bladder cancer is essential, as it dictates treatment approaches and influences patient outcomes significantly. However, despite the importance of TURBT, certain challenges persist, particularly concerning the accurate staging of high-grade superficial bladder tumors. High-grade non-muscle invasive bladder Ca (NMIBC), especially T1 and Ta high-grade tumors, presents risk of incomplete staging and persistent disease. Studies have reported persistent disease in 33% of patients with T1 tumors and 41.4% of those with Ta high-grade tumors, even when detrusor muscle is included but not

invaded in the initial TURBT. Furthermore, there is considerable upstaging risk at re-resection, ranging from 4% to 25%, and up to 45% when muscle is absent in initial specimen. Given these findings, both the 'European Association of Urology' (EAU) and 'American Urological Association' recommend a restaging TURBT for all T1 and high-grade tumors. However, implementing routine restage TURBT poses significant challenges, particularly in resource-constrained settings typical of tertiary care centers in India. The logistical demands, costs associated with repeat surgeries, and potential complications such as bladder perforation and stricture must be carefully considered. Additionally, patient compliance poses a significant barrier. Factors such as the temporary resolution of symptoms, reluctance to undergo repeat procedures within a short time frame, and logistical constraints like limited operating room availability contribute to non-compliance and patient dropout. These challenges highlight the need for a more rational approach to restage TURBT, especially in settings with limited resources.

This study aims to explore the necessity of re-resection in high-grade NMIBC, emphasizing the potential to refine patient selection criteria. By identifying tumor characteristics that can guide the requirement or exemption for restage TURBT, this research seeks to optimize resource utilization and improve patient outcomes. The goal is to provide evidence-based recommendations that balance the clinical benefits of re-resection with the practical constraints faced by healthcare providers and patients, ultimately enhancing the management of high-grade NMIBC in resource-limited environments.

AIM AND OBJECTIVE

Aim:

The present study was aimed to determine role of re-resection in high grade non-muscle invasive bladder cancer.

Objectives:

1) To assess the clinical value of reTURBT in patients stratified by clinical indications.
2) To compare the safety of TURBT and reTURBT.

REVIEW OF LITERATURE

Bladder Cancer

Bladder cancer, a malignant neoplasm of the urinary bladder, is the twelfth most common malignancy globally with more than 200,000 estimated deaths in 2018 (Bray et al., 2018). [10] Age-standardized incidence rates, however, differ considerably depending on sex and country. Males are more affected with bladder cancer than females and the incidence rates in countries with a low development index are less than a third compared to the ones in industrialized countries. In the province of Ontario (Canada), bladder cancer is currently the fourth (males) and sixth (females) most common cancer (Cancer Care Ontario et al., 2018). [11] With a median age at diagnosis of 73 years and > 90% of individual diagnosed after 55 years, bladder cancer is generally a malignancy of elderly. Smoking is the most important risk factor and is assumed to account for close to 50% of all incident cases (Freedman et al., 2011). [12] Both gender- and country-specific variation in smoking trends and occupational exposure are thought to explain a considerable amount of the heterogeneity encountered in incidence rates. Other risk factors are genetic predisposition, environmental pollution, prior medical conditions, and socio-economic parameters (Burger et al., 2013). [13]

From a histological perspective, bladder cancer can be divided into urothelial and nonurothelial histology. Urothelial carcinomas originating from the mucosa of bladder have a high propensity for divergent differentiation (e.g. squamous differentiation) and morphologic variants (e.g. micropapillary variant), reported to be 30% (Humphrey et al., 2016). [14] In contrast, pure non-urothelial bladder malignancies (e.g. squamous cell carcinoma, adenocarcinoma, sarcoma, or small-cell carcinoma) are generally rare (less than 5%) but have important prognostic and therapeutic implications (Dahm et al., 2003). [15]

Two internationally accepted systems have been in use to grade urothelial carcinomas. The WHO published in 1973 a three-tier grading system that distinguished between well differentiated (G1), moderately differentiated (G2), and poorly differentiated (G3) carcinomas (Mostofi et al., 1973). [16] Unfortunately, the WHO 1973 grading system has a high intra- and inter-observer variability and most UrothelialCa are categorized as G2 tumours (Soukup et al., 2017). [17] With the aim to reduce variability and to increase reproducibility, the ISUP introduced a grading system in 1998 that was taken up by the WHO in 2004 and slightly revised in 2016 (Moch et al., 2016).[18] The so-called WHO 2004/2016 grading system distinguishes between PUNLMP, low-grade urothelial carcinomas, and high-grade urothelial carcinomas. By restricting the grade spectrum of UrothelialCa to only two categories, the WHO 2004/2016 system partially mitigates problems associated with the WHO 1973 system (Soukup et al., 2017). [17]

Table 1: Staging of Tumors in Ca Bladder (Edge et al., 2010) [19]

TX	Primary tumor cannot be assessed
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumor invades lamina-propria
T2	Tumor invades muscularis-propria
T2a	Tumor invades inner half muscularispropria
T2b	Tumor invades outer half muscularispropria
T3	Tumor invades perivesical tissue/fat
T3a	Tumor invades perivesical tissue microscopically
T3b	Tumor invades perivesical tissue macroscopically
T4	Tumor invades prostate, pelvic wall, or abdominal wall
T4a	Tumor invades adjacent organs
T4b	Tumor invades pelvic side wall and/or abdominal wall

Bladder cancer is classified according to traditional AJCC's TNM staging. The anatomical extent of disease is classified by the TNM staging system as jointly developed by the 'Union for International Cancer Control' (UICC; 8th edition; 2017) (Union for International Cancer Control, 2017) and the 'American Joint Committee on Cancer' (AJCC; 8th edition; 2017) . The first component (T) defines the local extension of the primary tumour while the second (N) and third (M) components characterize extension to regional lymph nodes and distant metastasis, respectively. Carcinomas confined to either the mucosa (Ta, Tis) or sub-epithelial connective tissue (T1) are often summarized as non-muscle invasive bladder Ca although these tumor types considerably vary with respect to biology and prognosis. In contrast, the term muscle-invasive bladder Ca is said to be for tumours that invade the actual bladder muscle (T2, T3, T4).

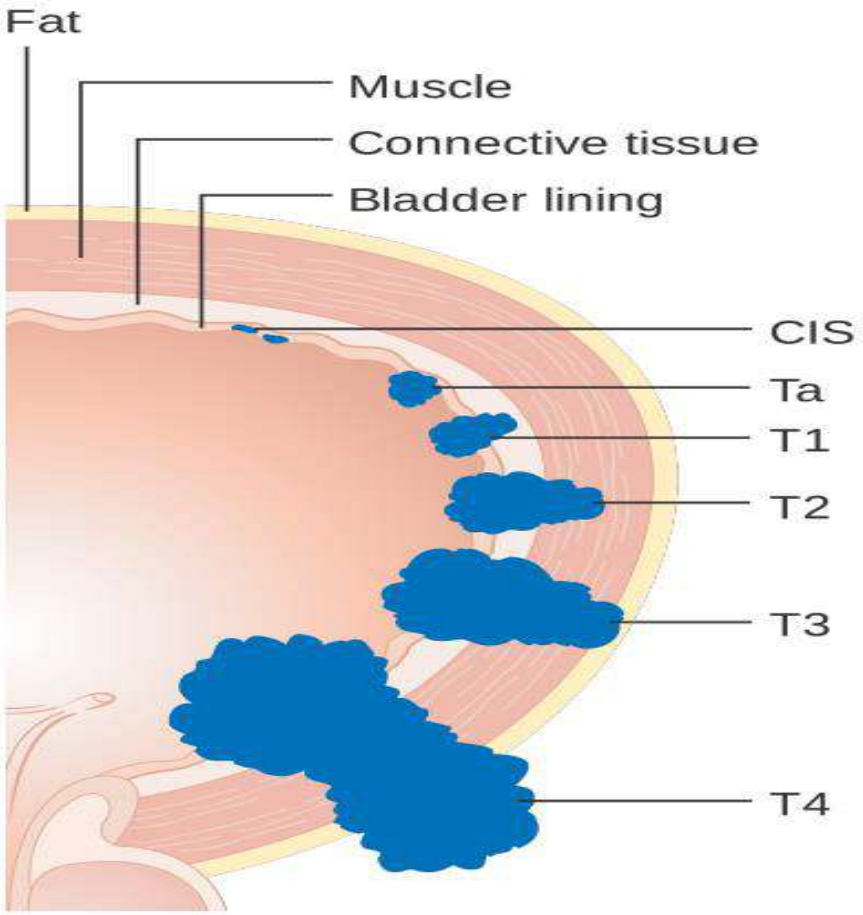

Figure 1: T stages of bladder cancer

At initial presentation, the majority (90%) of bladder cancers are characterized by localized growth, restricted to the various layers of the bladder wall, and among these localized tumors (≤T2), a substantial proportion (75%) are classified as non-muscle invasive, comprising carcinoma in situ (Tis), papillary urothelial neoplasms of low malignant potential (Ta), and tumors invading the lamina propria (T1) (Burger et al., 2013). [13] Based on distinct TNM criteria, the AJCC developed prognostic stage groups ranging from 0A (TaN0M0) with very favourable 5-year survival rates of 96% to IVB (anyTanyNM1b) where only 5% patient survive. In addition to non-muscle invasive bladder cancer and muscle-invasive bladder cancer, clinicians also use the terms localized bladder cancer (0a to II), locally advanced bladder cancer (IIIA to IVA) and metastatic bladder cancer (IVB) to group patients according to similar prognostic stage groups.

Non-muscle-invasive bladder cancers (NMIBC)

NMIBCs are low-grade papillary tumors that are caused by minor dysplasia or simple hyperplasia. Additionally included in this category is carcinoma in situ (CIS), a high-grade malignancy that is superficial (Kaseb et al., 2024). [20]Of the 82,000 new instances of bladder cancer expected to be diagnosed in the United states in 2023, NMIBC accounts for about 75%. Bladder cancer is the fourth most common malignancy of men and is more common in men than in women, with a ratio of about 3:1. Males are expected to make up the majority of the 16,700 projected deaths in 2023 (Siegel et al., 2023). [21] Although epidemiological data specific to non-small cell bladder cancer (NMIBC) are scarce, they can be inferred from data on bladder cancer, of which 75% were NMIBC at the time of presentation (Kamat et al., 2016).[22] 2020 saw the greatest age-standardized incidence rates (ASIR) of bladder cancer (and, consequently, NMIBC) across Western and Southern Europe. The regions with the

lowest ASIR were Central America, West and Middle Africa, and portions of Central and Eastern Europe (Sung et al., 2021). [23]

Patients with NMIBC have a rather good prognosis for survival; at ten years, the cancer-specific survival rate for high-grade disease ranges from roughly 70 to 85%, whereas the rate for low-grade disease is significantly higher (Palou et al., 2012). [24] Since they are significant factors in determining the long-term outcome, the recurrencerates and progression to MIBC are significant surrogate endpoints for prognosis in NMIBC. On the other hand, NMIBC is a clinically diverse collection of tumors that vary greatly in their chances of development and recurrence, depending on a number of pathologic and clinical variables. In the case of low-grade Ta lesions, for instance, long-term follow-up shows a recurrence rate of about 55%, but a far smaller proportion (6%) experience stage advancement (Leblanc et al., 1999). [25]In a single institution series, high-grade T1 lesions had a higher likelihood of progression (17%) and a large risk of recurrence (45%) (Palou et al., 2012). [24] Prognostic importance therefore arises from the capacity to forecast progression and recurrence risk in NMIBC based on patient-specific disease features. Personalized treatment choices and surveillance plans are aided by risk stratification in NMIBC as opposed to a generic, "one-size-fits-all" method.

Risk Factors of NMIBC

The commonest risk factor of bladder cancer is age, besides others. Bladder cancer is considered as an illness of the elderly, with a median age at diagnosis of about 70 years (Shariat et al., 2010). [26] Its incidence rises with age. For instance, age-specific incidence peaked in the 85–95 year age group, according to data from California (Schultzel et al., 2008). [27] The longer cumulative environmental exposure to carcinogens and the longer time available for the genesis and accumulation of cellular processes causing neoplastic transformations are the reasons for the

association between the incidence of bladder cancer and age. Additionally, older people may find it more difficult to completely empty their bladder, which prolongs the time when carcinogens released in urine come into touch with the bladder. Moreover, trouble urinating may cause elderly.

Another risk of the incidence and mortality of bladder cancer is gender of the patients. According to Dobruch et al. (2016) [28], males are 4 times more affected than females by bladder cancer, as evidenced by men predominating in the gender split in the majority of clinical and epidemiological studies. This disparity is the cause for varying exposure to risk factors, and it might be caused by variations in the metabolism of carcinogens and sex hormones. Men's outcomes aren't always worse, though, because women tend to present later and with more established illness. This could point to a lack of diagnosis, especially when hematuria is assessed, and therapy that disadvantages women (Dobruch et al., 2016). [28]

According to Cumberbatch et al. (2018) [29], smoking is a major behavioral risk factor. According to van Osch et al. (2016), the population-attributable risks of bladder cancer in Europe range from 37% to 20% in China. Smoking was expected to be responsible for 37% of bladder cancer disability-adjusted life years worldwide in 2019 (Safiri et al., 2021). [30] Additionally, bladder cancer risk may increase with lifetime exposure to secondhand smoke (Yan et al., 2018). [31] There may be dose-dependent relationship between smoking and recurrence as supported by the correlation between an elevated NMIBC recurrence risk and longer smoking duration and more pack-years (Kwan et al., 2022). [32]

The connection between diet and bladder cancer is studied. Many studies have investigatednumerous components of diet, such as the consumption of meat, vegetables, and fruits, the intake of vitamins, the amount of fluids

consumed, including coffee and tea, and the consumption of a Mediterranean diet (Zuniga et al., 2020). [33] A Western diet may be linked to a higher chance of NMIBC recurrence, but a diet high in red and processed meat may be linked with more risk of bladder cancer (Westhoff et al., 2018). [34]

Men's total cholesterol intake may influence with bladder cancer risk, while monounsaturated fatty acids may be linked to a lower risk of NMIBC. According to reports, drinking beverages and consuming sodium are linked to bladder cancer-specific survival and also overall survival in NMIBC (Leeming et al., 2022). [35]There was no correlation found between the overall quality of nutrition and the survival of bladder cancer patients. Overall, there is still a lack of evidence for many dietary risk factors because many studies are small, may be biased, or have inconsistent findings among reports, making them difficult to interpret (Cumberbatch et al., 2018).[29] Research has demonstrated that cohorts diagnosed with bladder cancer exhibit lower levels of physical activity compared to the age-matched general population. This decrease in physical activity is linked to greater body mass index (BMI) and increased smoking exposure (Catto et al., 2023). [36]

Research on the microbiome's predictive and maybe therapeutic significance in bladder cancer is likewise becoming more and more intense. Abundance of various genera in healthy individuals and those with Ca bladder or NMIBC is examined, primarily using tissue and urine samples (Zhang et al., 2023). [37] Small studies still make up the majority of the evidence base, which at this point points to the microbiome's rather narrow involvement in illness prediction.

Diagnosis

For bladder cancer to be properly treated, a precise diagnosis must be made. A thorough history is first step for making a diagnosis. Examining symptoms and doing a targeted physical examination could reveal information indicating a more advanced stage of the illness. According to Lammers et al. (2011) [4], offering patients advice on quitting smoking after receiving a diagnosis can lower their risk of intra operative and post operative complications as well as chance of an NMIBC recurrence.

The diagnosis of bladder Ca is visually validated by office-based cystoscopy, which is done by anesthesia-induced TURBT. Staging by TURBT requires detailed descriptions of the tumor's size, location, no.of lesion, architecture, and related changes. The objective of all TURBTs should be resection of tumor with safe sampling of the muscle layer, as this improves oncologic outcomes and histopathologic accuracy. The performance of repeat transurethral resection of bladder tumor (TURBT) has been shown to confer significant advantages in diagnostic accuracy, prognostic assessment, and therapeutic outcomes, and is therefore widely recommended as a standard procedure for all high-grade bladder malignancies, especially in cases where the initial pathology specimen is devoid of a detrusor muscle layer, thereby precluding comprehensive staging (Herr et al., 1999) [3]

Standard cross-sectional imaging with delayed drainage films enables the evaluation of synchronous or metastatic upper tract disease. However, CT or MRI urography remains the gold standard for comprehensive assessment of the upper tracts, lymph nodes, and abdominopelvic viscera. Additionally, chest imaging is essential to exclude pulmonary metastases, particularly in smokers who are at elevated risk of secondary primary malignancies.

Novel imaging techniques like ‘hexaminolevulinic acid-blue light cystoscopy’ or fluorescence cystoscopy using either 5-aminolaevulinic acid (5-ALA) are becoming popular day by day. When fluorescence cystoscopy is used instead of traditional white light cystoscopy (WLC), it can discover extra primary tumors that WLC misses in about 20% of patients, and it has shown better sensitive for detecting carcinoma in situ (CIS) (Daneshmand et al., 2014). [38] When comparing HAL-BLC with WLC, meta-analyses shows benefits in recurrence rates but not in progression or fatality rates (Daneshmand et al., 2018). [38] While previously false-positive rates observed with regular WLC have not differed significantly, higher rates of false-positive outcomes with BLC can reduce specificity. Another improved cystoscopy method to help with the contrast images is narrow-band imaging.

Because some CIS can not be with traditional WLC, urine cytology is also a useful addition to tumor inspection and biopsy. Urine cytology is not recommended for low-risk NMIBC and normal cystoscopy since it performs poorly with low-grade tumors (0.04-0.30) and is more sensitive to high-grade cancers like CIS (0.80).

Few biomarkers have shown themselves to be accurate making them fit for routine use in place of cystoscopy, with sensitivities ranging from 0.57–0.82 and specificities between 0.74–0.88 (Chou et al., 2015). [39] The established interobserver variability of pathologic evaluation presents problems to the histopathologic diagnosis of NMIBC. Consequently, it is the urologist's responsibility to give the pathologists the best specimen possible that is free of crush injuries and cautery. The most crucial stage in diagnosing and treating NMIBC is methodical and thorough visual resection with either fractioned or en bloc excision that sufficiently resect the detrusor muscle.

When paired with TURBT alone, adjuvant intravesical therapies reduce the progression risk and recurrenceriskalso. Adjuvant intravesical therapy is generally safe, but its usage is predicated on a risk-adapted strategy that tries to strike a balance between the prevention of progression and recurrence and the side effects—especially systemic—of overtreatment. To measure the recurrencerisk and progressionrisk, many clinical and pathological variables are used in various risk stratification techniques. A patient-centered discussion regarding adjuvant treatment choices should be initiated to guide the next stages, knowing each patient's unique cancer risk profile following TURBT and knowing their comorbidities.

Risk stratification is influenced by various factors, including the existence or lack of variant histology, concurrent CIS, and lymphovascular invasion. These factors may lead to the decision to consider radical cystectomy as an upfront treatment, notintravesical therapies.

Risk Stratification of NMIBC

Since NMIBC is diverse subclassification of bladder cancer, care should be tailored to the patient's needs. The likelihood of recurrence for any patient at one year can vary from 15% to 70% based on the features of the tumor (Sylvester et al., 2006).[40] When compared to TURBT alone, adjuvant intravesical therapy following TURBT effectively lowers the recurrencerisk and risk of development of NMIBC, as evident by multiple studies and ensuing meta-analyses (Shelley et al., 2003).[41] Since every intravesical therapyarenot equally effective or recommended across risk categories, current adjuvant treatment techniques are risk tailored.

Many available techniques for stratification, such as nomograms,which are useful in establishing personalized risk projections for progression and recurrence. These tools were produced using post hoc analysis of data gathered during large-scale randomized, controlled trials (RCTs) by

CUETO and the EORTC. As a result, each can determine the unique risks of progression and recurrence. All of these nomograms are validated and spare patients from being arbitrarily categorized into large risk groups. However, it's crucial to comprehend and take into account some of the limitations associated with their utilization.

Table 2: Comparison of Risk Factors Used in Nomograms

EORTC	CUETO
Number of tumors	Gender[a]
Tumor size	Age
Recurrent tumor	Recurrent tumor
T stage	T stage
Concurrent CIS	Association CIS
WHO grade	WHO grade

78% of patients were treated mainly with various intravesical chemotherapy regimens, and no patient underwent a second TURBT. Of the patients, none received maintenance therapy, and only 6.5% received BCG. Based on data from 1062 patients who were given BCG in 4 randomized trials, the CUETO group created a comparable nomogram (Fernandez-Gomez et al., 2009).[42]

The CUETO cohort's use of maintenance therapy was restricted to a period of five to six months. The EORTC then created a nomogram and extra risk classes in 2016 for a pooled cohort of patients from two RCTs evaluating the benefit of BCG maintenance for one to three years in 1812 intermediate- and high-risk individuals (all without CIS). Tumor grade is an additional predictive factor for early recurrence.

Clinical outcomes in NMIBC

Clinical outcomes differ across risk groups and countries, as well as by treatment and healthcare system.

The 5-year recurrence-free survival ranged from 17–89%, progression-free survival (PFS) from 58–89%, cancer-specific survival from 71–96%, and overall survival (OS) from 28–90%, according to recent systematic review of real-world evidence studies of patients with high-risk NMIBC (Musat et al., 2022). [43] According to this review, patients who underwent and successfully finished intravesical therapy with BCG had more survival than those without BCG. More information about patients receiving appropriate BCG therapy for intermediate- and high-risk NMIBC (Kamat et al., 2016)[22] confirmed exceptional 5-year survival rates, with RFS of 86% and 72%, PFS of 100% and 91%, and OS of 79% and 87% for patients at intermediate and high risk, respectively (Matulay et al., 2021).[44] Similarly, a US cohort of patients with high-risk NMIBC demonstrated a 10-year PFS of 78% after receiving appropriate BCG induction treatment (Williams et al., 2021). [45]

More generally, for US patients between 1988 and 2006, median survivability estimates of 5.3 years (95% confidence interval (CI) 5.2 to 5.4 years) and 4.4 years (95% CI 4.3 to 4.6 years), respectively, were published (Seo et al., 2018). [46] According to age, sex, and race/ethnicity, survivorship varied in this US analysis, with older and non-white patients having shorter survival times. Over a median follow-up of 63 months, 59% of patients in Sweden with intermediate-risk NMIBC had a recurrence (Wang et al., 2022). [47]

Treatment/Management of high-risk NMIBC

National and international groups are issuing an increasing number of guidelines for the treatment of NMIBC. These recommendations' quality vary, especially in terms of application, development rigor, and stakeholder involvement (Maisch et al., 2021). [48]

TURBT is the initial step for addressing NMIBC after patient assessment and work-up (Babjuk et al., 2022).[6] The therapeutic objective of TURBT should be the removal of all visible tumors, and the diagnostic goal should be the completion of disease staging.Based on location and size of the tumor, fractioned or en-bloc procedures may be performed. Although the relative benefits of each approach are still up for debate, en-bloc resection might be linked to shorter catheterization and hospital stays without affecting the frequency of complications. The presence of detrusor muscle in the material is a surrogate criterion for resection quality and a necessary component of TURBT in all cancers other than Ta G1/LG tumors and its absence is linked to markedly increased risks of tumor understaging, early recurrence, and residual disease.

White light is mostly used for cystoscopy during TURBT. Blue light cystoscopy, commonly referred to as photodynamic diagnostics (PDD), is a more modern substitute that makes use of an intravesically injected photosensitizing chemical that preferentially accumulates in tumor cells so that the latter may be identified by their fluorescence (Heer et al., 2022).[49] PDD has a better sensitivity but a lower specificity when it comes to detecting bladder cancer than white light cystoscopy (WLC). Because PDD can detect tumors more accurately, its use may influence treatment choices. According to guidelines, the AUA/SUO guideline now recommends using PDD over WLC, but the EAU guideline recommends using PDD sparingly (Babjuk et al., 2022[6]). Compared to WLC, blue light cystoscopy may be associated with lower risks of disease progression and recurrence, according to systematic reviews and meta-analyses. Given the limitations in the body of current information, such as the inconsistent application of adjuvant therapy, the advantages of PDD may depend on baseline risk and the results were unclear (Maisch et al., 2021). [48]

The recently published PHOTO RCT, which compared standard WLC TURBT with TURBT guided by PDD in 538 patients with NMIBC across UK centers, was not included in these reviews. This study found that, there was no discernible difference between bladder cancer-specific or overall survival rates between PDD-guided and conventional WLC TURBT in terms of recurrence or progression risk. PDD-guided TURBT was likewise not expected to be more economical than WLC TURBT after three years. The authors came to the conclusion that treating patients with primary intermediate- or high-risk NMIBC could not be accomplished with PDD-guided TURBT (Heer et al., 2022). [49]

Nonetheless, the trial has caused significant debate due to its discrepancies from the body of current research. The trial has drawn criticism in particular for underpowering to detect differences between PDD and WLC because its power calculations relied on risk reductions that were deemed insufficient, and because the planned patient accrual had not concluded by trial's end. Additionally, a significant portion of randomly assigned patients were excluded fromanalysis. Furthermore, a greater proportion of patients in the WLC arm got adjuvant therapy, including BCG, indicating that adjuvant therapy was not evenly distributed across study arms. Additionally, it was thought that the trial's high-risk patient population was underrepresented (Stenzl et al., 2023).[50] Considering the correlation between elevated baseline risk and increased benefits of PDD, it is likely that the majority of the intermediate-risk group analyzed in PHOTO

The trial's failure to find differences between PDD and WLC may have been because to variations in TURBT quality, which are impacted by surgeon experience. Stenzl et al. (2023) [50] came to the conclusion that the PHOTO trial would not undermine the available data supporting PDD in NMIBC in light of these considerations.

Table 3: General Management of Bladder Cancer According to Disease Stage

Disease stage	Management
Localized NMIBC (0a, 0is, and I)	TURBT with or without intravesical immuno- or chemotherapy Radical cystectomy for tumors at high to highest risk for progression to MIBC
Localized MIBC (II)	Radical cystectomy and perioperative chemotherapy (neoadjuvant or adjuvant) Trimodal therapy
Locally advanced MIBC (III A and III B)	Resectable disease Radical cystectomy and perioperative chemotherapy (neoadjuvant or adjuvant)
Locally advanced MIBC (IV A [T4banyNM0])	Unresectable disease Cisplatin-based chemotherapy (first-line) for fit patientsa Immunotherapy for unfit patients or for individuals who progressed under a cisplatin-based regimen Best supportive care (decompression of upper urinary tract, control of pain and bleeding)
Metastatic disease (IV A and IV B)	Cisplatin-based chemotherapy (first-line) for fit patientsa Immunotherapy for unfit patients or for individuals who progressed under a cisplatin-based regimen Best supportive care (decompression of upper urinary tract, control of pain and bleeding)

Single, immediate post-operative instillation of chemotherapy

It is advised that the first adjuvant treatment following TURBT begin with a single, timely chemotherapy infusion within 24 hours of the operation, ideally within 2 to 6 hours (Babjuk et al., 2022). [6] Regardless of adjuvant BCG therapy, a "single shot" of MMC or gemcitabine has shown to lower incidence of recurrence in individuals with NMIBC across all risk groups. Patients with low-grade Ta tumors respond best to a single post-TURBT chemotherapy infusion (Sylvester et al., 2016). [40] There is no need for anyinterventionin low-risk patients after this initial instillation.

Intravesical BCG

Chemotherapy or intravesical BCG treatment is the subsequent adjuvant treatment for patients at intermediate and high risk (Babjuk et al., 2022). [6] NMIBC is mostly treated intravesically with BCG, a live attenuated strain of Mycobacterium bovis, via immunotherapy. Clinical investigations have shown BCG as a safe and efficient way to slow the growth and recurrence of tumors. There are other strains of BCG that are equally safe and effective (Babjuk et al., 2022). [6]

Most of guidelines advise administering BCG according to the SWOG, or "6+3," schedule. In high-risk patients, maintenance treatment consists of three instillations (one instillation per week over three weeks) at three and six months, and then every 6 months thereafter, for a maximum of thirty-six months from the start of induction therapy. The induction period lasts for six weeks. The same induction regimen is applied to individuals at moderate risk, but maintenance is cut to one year, with three injections given at three, six, and twelve months (Babjuk et al., 2022). [6]

Clinical practice and research do not always follow the SWOG protocol, and many interventional studies simply take into account induction therapy or alter the frequency, duration, or dosages of BCG (Tabayoyong et al., 2018). [51]

Intravesical chemotherapy

In high risk NMIBC, intravesical chemotherapy is an option to BCG, especially for recurrent NMIBC(Taylor et al., 2020). [52] In patients with recurrent intermediate-risk NMIBC, pre-operative/neoadjuvant use of intravesical chemotherapy with MMC (sometimes called "chemoresection") has been proposed to assist lower number of invasive operations (TURBT). Apart from MMC, other chemotherapy that are now in use are docetaxel, gemcitabine, and epirubicin.

Sequential gemcitabine-docetaxel has been studied as an alternative or salvage therapy in NMIBC because of the scarcity of BCG. Retrospective examinations of high-risk patients who were either BCG naïve or had failed BCG revealed that this sequential instillation treatment was successful and well-tolerated (McElree et al., 2022). [53] When comparing gemcitabine-docetaxel to BCG for treatment-naïve high-risk patients, a comparative retrospective research found better results and lower treatment dropout rates (McElree et al., 2023).[53] The interpretation of these data is limited, nevertheless, by the comparison of modern gemcitabine-docetaxel patients with a historical BCG cohort, which had differing follow-up intervals and used a non-standard reduced-dose BCG-IFN-2α combo treatment as a comparator.

Urologists are now compelled by a lack of BCG to look into methods for enhancing the delivery of chemotherapy more effectively. Since enhanced antitumor effects are demonstrated, the idea of device-assisted intravesical therapy—specifically, chemohyperthermia, also known as hyperthermicintravesical chemotherapy (HIVEC) or radiofrequency-induced thermo-chemotherapy effect (RITE)—to improve the penetration of MMC and other chemotherapeutic agents into the bladder wall seems promising. Nevertheless, intravesical device-assisted chemotherapy is not

widely accessible for NMIBC patients, despite data mounting in the BCG-naïve and BCG-unresponsive settings (Zhao et al., 2021). [54]

Radical cystectomy

The most effective treatment for MIBC is radical cystectomy, and in patients with very high-risk NMIBC, early radical cystectomy is the recommended course of action. However, new research also points to a potential clinical advantage of intravesical BCG in these patients. For BCG-unresponsive illness, an early radical cystectomy is also advised (Babjuk et al., 2022)[6]. Although the high-risk traits that determine eligibility for radical cystectomy vary among guidelines, research assessing the advantages of an early radical cystectomy have not differentiated between individuals who has not responded to BCG and those who have. Therefore, it's uncertain if early radical cystectomy is beneficial for patient who have never taken BCG. Although the BRAVO-Feasibility research showed that patients with high-grade NMIBC treated with an early radical cystectomy had satisfactory outcomes, it was deemed unlikely that more patients could be recruited for a bigger trial given the

Repeat TURBT

The second (-look) TURBT should be carried out 4-6 weeks following the initial resection if the first TURBT is not complete or if the specimen lacks detrusor muscle (Babjuk et al., 2022).[6] While AUA/SUO guidelines advocate repeat TURBT in high-risk Ta HG tumors as well as T1 tumors, EAU guidelines only take T1 tumors into consideration for repeat TURBT. Guidelines that support re-resection are based on repeated results indicating, in patients with high-risk or high-grade NMIBC, second TURBT enhances response to intravesical BCG and lowers the risk of recurrence (Regnier et al., 2022). [55] Additionally, data indicates that in patients with T1 bladder cancer, a second TURBT is associated with improved all-

cause mortality (but not cancer-specific death). There seems to be no difference in survival between re-TURBTs were out before to and following

The restaging TURBT was the main focus of the current investigation. NMIBC is a cancer that progresses rapidly and presents complications due to understaging and muscle invasive disease. The quality of the initial TURBT is crucial, as was previously mentioned. It is therefore not surprising that, in a study, it identified the potential benefits of a second TURBT prior to the first cystoscopic follow-up appointment at three months as early as 1994. In the literature, this second TURBT—henceforth known as re-resection—is also known as re-TURBT, re-staging TURBT, secondlook TURBT, or re-look TURBT. Re-resection within two to six weeks following the initial TURBT is currently a vital part of majority of NMIBC recommendations (Babjuk et al., 2019).[6]

Comparing to patients who underwent re-resection after six weeks but before 90 days, those who received re-resection between two to six weeks had superior recurrence-free (73.6% compared 46.2%) and progression-free (89.1% against 79.1%) survival. Moreover, even after knowing for age, sex, stage, grade, concurrent carcinoma in situ, tumor size, immediate postoperative intravesical chemotherapy, tumor status (primary versus recurrent), and tumor focality (solitary versus multiple), the time interval between the initial TURBT and re-resection was linked to both recurrence and progression rates. This sample may not be typical of all people with T1 bladder cancer, but it did offer valuable information on when to perform a resection.

In a study by Gendy et al. (2016)[56], the re-resection rates of 162 patients with T1 tumors from Australia were examined. Out of them, 29.6% had their tumors removed within eight weeks. Re-resected patients had a

decreased three- to six-month recurrence rate (39.6% versus 84%). However, the unadjusted comparison (confounding bias) and possible selection bias (excluding of upstaged patients) place limitations on these estimations.

The largest cohort study examining the function of re-resection in T1 bladder cancer was done by Gontero et al. (2016). [7] The authors observed 2,451 T1 tumors, of which 38.1% underwent excision within four to six weeks after receiving a complete induction dose of BCG therapy. Re-resected patients showed increased overall, cancer-specific, recurrence-free, and progression-free survival in analysis, but only if detrusor muscle was not sufficiently sampled during initial TURBT. Further, patients who underwent TURBT, had higher odds of having multiple tumors at the initial TURBT, were younger, and had a lower likelihood of having a sufficiently sampled detrusor muscle. Initially, selection bias can be introduced by the manner the group was selected (T1 tumors with a full induction course of BCG therapy). To be more precise, patients chosen for radical cystectomy based on the re-resection outcome and never got the entire induction dose of BCG therapy were excluded, artificially increasing the prognosis of the re-resection arm (inclusion criterion). Second, the results are susceptible to confounding bias since models were little modified for confounding factors.

Gotto et al. (2016) [57] presented a population-based study that examined T1 bladder re-resection in the Canadian province of Alberta. Out of 600 patients with T1 bladder cancer that the scientists tracked, 27.8% had resections within three months. Between 2007 and 2011, the percentage of patients undergoing re-resection rose from 27.4% to 37.8%. Younger age, site of the first TURBT (instead of Calgary), and the year of diagnosis were independent variables linked to the receipt of re-resection. Patients who had resection showed better overall outcome over a five-year period

(72.7 versus 55.3%) in an unadjusted study. Given that patient age was the only adjustment factor used in multivariable analysis, confounding bias clearly has an impact on the survival results of this investigation. However, it should be highlighted that the authors also included patients which were upstaged at re-resection, which makes them different from previous research. Consequently, there may be little chance of selection bias.

Patschan et al. (2017)[58] carried out a population-based comparison analysis in Sweden. Of the 903 patients with T1 bladder cancer, 55.7% had a resection done in less than eight weeks. Younger age, greater tumor grade, multidisciplinary tumor conference, and higher hospital volume were factors that were linked to re-resection. Re-resection was linked to better cancer-specific survival, but this link vanished when factors such as age, gender, tumor grade at initial TURBT, healthcare region, multidisciplinary tumor conference, number of hospitals, and intravesical treatment were taken into account. By including patients who were upstaged at re-resection, the authors of the population-based study from Alberta, Patschan et al. (2017) [58], avoided selection bias. The group of patients who did not receive re-resection would eventually have an artificially poor prognosis if immediate cystectomy patients, who had a comparatively worse prognosis, were assigned to the "no re-resection" arm. The Swedish study's authors modified their survival models to account for a greater number of assumed confounders than their Canadian counterparts (Gotto et al., 2016). [57] These included hospital volume (dichotomized), age (dichotomized), gender, tumor grade, healthcare region, availability of a multidisciplinary tumor conference, and intravesical treatment. Nevertheless, the final estimate is still susceptible to residual unmeasured confounding bias because it isin a population-based study conducted in the UK's South Yorkshire region, Gordon et al. (2019) [59] monitored a cohort of 932 individuals with bladder cancer that was not muscle invasive. Re-resection rates were as low as 20% in 1995,

but by 2007, they had nearly risen to 80%. The results of Kaplan-Meier analyses, patients who had re-resection within three months (24.6%) had lower odds of dying from any cause (19.8% compared 80.1%) and bladder cancer (22.2% against 77.8%). Nevertheless, their likelihood of developing muscle-invasive illness was higher (27.2% compared to 10.5%).

First, the matching log-rank tests and the p-values of the univariable models did not match. Secondly, the labels assigned to effect estimates were odds ratios rather than hazard ratios. Third, the multivariable models did not incorporate re-resection, which is the true exposure of interest. Consequently, their research only offers uncorrected estimates that are significantly impacted by confounding bias. Ten-year follow-up statistics were reported by Divrik al. in 2006. [5] Ten-year survival for progression-free patients (83.4% against 68.6%, p = 0.04), recurrence-free patients (48.5% compared 27.0%, p = 0.004), and overall patients (59.1% versus 40.8%, p = 0.04) all strongly supported re-resection, according to the updated (intention-to-treat) analysis.

The intention-to-treat analysis can be considered as a commendable attempt to repair the damaged internal validity of this trial. Unfortunately, the investigators still withheld valuable information required to judge the validity of this study and the correctness of the intention-to-treat analysis is questionable since the Kaplan-Meier estimate at ten years for the per-protocol analysis is not different from the one reported for the intention-to-treat analysis (59.1% versus 59.1%) although twelve patients, who had muscle-invasive disease at re-resection and therefore a 50% chance to survive five years (Cancer Research), were added to the re-resection arm (Eroglu et al., 2020). [60]

Review of relevant studies

A research by **Desai et al. (2024)** [61] sought to determine which patients with high-risk NMIBC may forego the often carried out restage TURBT procedure. Patients with biopsy-proven NMIBC who had gross complete

painless hematuria due to a urinary bladder mass were included in this prospective observational analysis. After two to six weeks of initial TURBT, patients with high-risk diseases will receive restage TURBT. The final study comprised a total of 250 individuals with histopathologically confirmed high-risk illness after re-TURBT (n = 237 with deep muscle involvement and n = 13 without muscle involvement). Eighteen percent of patients reported recurring or persistent tumors during re-TURBT. Upper tract modifications, perivesical fat stranding, tumor size greater than 3 cm, high-grade histology, and a positive urine test for malignant cytology all had an upstaging. Even though the probability of tumor recurrence in restage TURBT is low, restage TURBT performed 2-4 weeks after primary TURBT is crucial for accurately diagnosing NMIBC patients. This helps patients with upstaging and recurrent/residual tumors even more in determining the next course of treatment.

The viability of an RCT comparing the effects of immediate reTUR plus adjuvant Bacillus Calmette-Guérin (BCG) against upfront induction BCG following initial TUR in NMIBC was evaluated by **Soria et al. in 2023.** [62] Random assignments were made to provide reTUR + adjuvant BCG or upfront induction BCG following TUR for eligible patients. Over the course of 14 months, 30 patients (15 per arm) were randomly assigned (August 2020–October 2021). With two eligible patients declining to be randomly assigned, the trial protocol had a patient compliance rate of 93.3%. Prior to randomization, they eliminated 49 patients who were made ineligible due to various reasons such as histological subtypes (n = 16, 33%), live donor absence in the TUR specimen (n = 9, 18%), metastatic disease (n = 5, 10%), concurrent UTUC (n = 3, 6%), or hydronephrosis (n = 4, 8%). Upon reTUR, disease recurrence was found in three patients (23%) in the reTUR arm and six patients (40%) in the upfront BCG arm throughout the course of a median follow-up of 17 months. One patient receiving upfront BCG treatment showed signs of progression to muscle-invasive illness. It has been proved that it is feasible to perform an RCT in high-grade T1

NMIBC that compares upfront BCG to reTUR + BCG. These findings highlight the necessity of screening a large number of patients because a high percentage of cases have characteristics that match the exclusion criteria.

To determine the predicted criteria for BCG response in patients diagnosed with high-grade non-muscle invasive bladder cancer, **Ferro et al. (2022)** [63] performed a retrospective analysis. Enrolled were 1,228 patients with Ca bladder that was not muscle invasive. 20.9%, or 257 individuals, did not respond to BCG. Multifocality (HR: 1.4; 95% CI 1.05–1.86; P = 0.019), lymphovascular invasion (HR: 1.75; 95% CI 1.22–2.49; P = 0.002), and high-grade on re-TURB (HR: 1.39; 95% CI 1.02–1.91; P = 0.037) were independent predictors of responsiveness to BCG.At five and ten years, respectively, there was a significant difference in overall survival between BCG-unresponsive and BCG-responsive patients (82.9% vs. 92.4%, P < 0.0001) and 44.2% vs. 74.4%, P < 0.0001). Similarly, at 5 years (90.6% vs. 97.3%, P < 0.0001) and 10 years (72.3% vs. 87.2%, P < 0.0001), cancer-specific survival was worse in BCG-unresponsive patients. Re-TURB high-grade, multifocality, and lympho-vascular invasion were predictors of BCG therapy response. Patient not responding to BCG reported worse oncological outcomes.

According to **Hu et al. (2022)** [64], repeat transurethral resection of bladder tumors (reTURB) is advised by worldwide guidelines for certain patients with high-risk non-muscle invasive Ca bladder in order to eliminate any potential residual tumors, prevent recurrence of the tumor, and enhance the therapeutic outcome. Nevertheless, traditional TURB provides the majority of the data demonstrating reTURB's advantages. It is still uncertain what function reTURB serves in patients undergoing first En bloc resection of bladder tumors (ERBT).

In a prospective randomized research, **Demir et al. (2022)** [64] sought to determine the impact of the time to re-staging resection (re-TUR) on the rates of progression and recurrence in patients with high-risk non-muscle-invasive Ca bladder. Re-TUR timing was used to randomly divide the patients into three groups. The time span between the original and re-TUR was 14–28 days, 29–42 days, and 43–56 days for Groups 1, 2, and 3, respectively. The trial was completed by twenty patients in Group 1 (14–28 days), twenty patients in Group 2 (29–42 days), and twenty patients in Group 3 (43–56 days). The three groups' rates of PFS and RFS did not differ, according to Kaplan-Meier plots.Only tumor number was revealed to be a prognostic effect for RFS rates, according to Cox regression analysis. Time laps between the initial TUR and re-TUR did not significantly affect the RFS and PFS rates, as this prospective trial showed.

A study was carried out by **Paciotti et al. in 2021**[65] to report on long-term oncological result of en bloc resection (ERBT). This study is done after the fact using data that was found in the future.In total, 74 patients were involved in this investigation. Seventy-one was the median age (66–76). The median tumor diameter was 2 cm, and the majority of patients only had one bladder tumor when they first arrived. Following histological analysis, low-, intermediate-, and high-risk diseases were identified in eight, thirty-five, and thirty-one patients, respectively. The detrusor muscle was present in every tumor that was removed in one piece.

A follow-up of 72 months was the median. At the initial follow-up cystoscopy, four out of 74 patients had a recurrence rate of 5.4%. At five years, 57 (77%) of the patients had no recurrences. Progression-free survival was 100%; there were no evidence of progression to MIBC. The small size and retroactive design are among the limitations. These results demonstrated that the best long-term oncological outcome for NMIBC is ERBT.

The results of patient with high-grade non-muscle-invasive Ca bladder who underwent re-resection after their initial therapy and those who didn't were compared by **Gordon et a**l. in **2019**. [59] All eligible patients receiving treatment in Sheffield between 1994 and 2009 who had new diagnosis were includedin this study. 932 suitable patients were found in this study; 229 (or 25%) of them had resections within 12 weeks after the diagnosis, and 234 (or 25%) did so within 3 months. Clinicopathological standards for patients with and without re-resection were comparable. Following re-resection, histological results showed that 91(20%) patients had no residual cancer and 138(30%) had BC (15 low-grade, 85 high-grade, and 38 muscle-invasive tumors).

Compared to patients without re-resection, those who had re-resections were likely to have muscle invasion (126 [27%] vs 49 [11%], chi-square $p<0.001$) and to undergo drastic treatment (127 [27%] vs 35 [8%], $p<0.001$).A total of 207 patients—46 (22%) with and 161 (78%) without re-resection—died from BC. Compared to patients who didn't undergo re-resection, those who did had higher disease-specific (log rank $p=0.009$) and overall ($p<0.001$) survival. Only that cancer was diagnosed as pT1 showed differences. Within three months of diagnosis, patients who underwent re-resection had a greater survival rate, were more likely to have radical treatment, and had muscle invasion that could be recognized histologically. Patients having lamina-propria invasion showed the biggest changes, indicating that others may be able to avoid them.

Using a meta-analysis of the available data sets and a review of the literature, **Naselli et al. (2018)** [66] evaluated effect of reTUR in T1 bladder cancer. Out of all the papers found, 29 were chosen. The study population for the assessment of the prevalence of residual tumor and upstaging,

respectively, consisted of a total of 3566 and 2556 patients. 1565 and 1187 were the matching numbers for the subgroup whose detrusor muscles were involved at the initial TUR. For residual tumor, the pooled prevalence was 0.56 (95% confidence interval [CI] 0.48–0.63), and for upstaging to T2 at reTUR, it was 0.1 (95% CI 0.06–0.14).
For the detrusor muscle subgroup, the comparable rates were 0.47 (95% CI 0.33–0.62) and 0.1 (95% CI 0.06–0.14). All of the studies that were looked at had an excessive influence, according to the sensitivity analysis. In T1 instances, the combined prevalence rates for residual tumor (about 50%) and upstaging to invasive disease (10%) at reTUR were substantial, consistent across studies conducted in various decades, and also held true for cases where the detrusor muscle was involved at the original TUR. Consequently, reTUR continues to be an essential process.

A comprehensive assessment of the use and therapeutic advantages of an early reTUR for high-risk NMIBC was conducted by **Cumberbatch et al. (2018)**. [29] After screening 15, 209 manuscripts, this study included 31, which included information on 8409 people with high-grade Ta and T1BC. In 30–100% of patients, detrusor muscle was seen at the initial TUR histopathology. After Ta, residual tumors were identified in 17–67% of patients, and after T1 cancer, in 20–71% of patients. 36–86% of the remaining tumors were discovered at the original site of excision. In 0–8% (Ta to ≥T1) and 0–32% (T1 to ≥T2) of cases, there was an upstaging. The effect of reTUR on later recurrence and cancer-specific mortality is reported in conflicting evidence. In the reTUR group, Ta recurrence was 16%, while in the non-reTUR group, it was 58%. There was no discernible correlation between reTUR and Ta advancement; however, in series with control populations, T1 rates were greater in the non-reTUR group (5/6 trials). In two studies with controls, there was a small reduction in overall mortality (22–30% vs. 26–36% [no reTUR]) in the reTUR group. The study found that in high-risk NMIBC patients, residual tumor is frequently found

following TUR. ReTUR aids in the detection of this residual malignancy and may help tumors that were originally staged as T1 to have better results.

Retrospective medical records of patients treated at 'Seoul National University' between October 2004 and December 2013 who had repeated TURBT within two to six weeks following a first resection were examined by **Tae et al. (2017)**. [67] Patients with muscle-invasive tumors on repeat TURBT were excluded from the study; patients with NMIBC diagnoses at both the initial and repeat TURBT were included. The independent impacts of the predictive factors were evaluated, and the estimated hazard ratios (HRs) from the Cox models were utilized in this analysis. A total of 198 patients with a diagnosis of high-risk NMIBC were examined in this study.

The number of bladder tumors (2–7: OR, 2.319; 8≤: OR, 3.353; $p<0.05$), the presence of carcinoma in situ lesion (OR, 3.639; $p = 0.017$), and the initially high tumor grade (OR, 2.435; $p = 0.040$) all showed correlations with the residual tumor in the repeated-TURBT specimen in logistic regression analysis. In multivariate analysis, T1 stage in repeated-TURBT strongly linked with both advancement (HR, 2.806; $p = 0.029$) and recurrence (HR, 1.837; $p = 0.010$). In the multivariate analysis, there was a significant correlation between the high grades of tumors in repeated-TURBT and progression, but not recurrence (HR 2.152; $p = 0.008$). The pathologic results in repeated-TURBT in study were linked with the development and recurrence of high-risk NMIBC. Repeated-TURBT is valuable because it can predict the recurrence and progression of high-risk NMIBC in addition to obtaining accurate pathologic findings.

The primary determinants of understaging in patients with T1G3 non-muscle invasive bladder cancer were assessed by **Minardi et al. (2016)**. [68] TURBT and radical cystectomy (RC) with dissection of pelvic lymph

nodedisscection were done on 109 patients with T1/G3. Many factors were taken into consideration when assessing the understaging detection. In RC samples, 35 (32.1%) patients had the proper staging, whereas 74 (67.9%) patients had muscle invasion, or understaging. This study found no correlation between clinical outcomes and factors like age, gender, tumor morphology, CIS association, or surgeon experience in patients having high-grade tumors. Conversely, understaging was linked to various tumor features, including invasion of the deep lamina propria, microscopic vascular invasion, multiple tumor foci, large tumor size (>6 cm), tumors located in the trigone or dome, and the presence of residual tumor.

In a modern Australian series, **Gendy et al. (2016)** [56] assessed the depth of transurethral resections of bladder tumors (TURBT), residual cancer rates, and up-staging rates. Analysis was done on 1,299 transurethral resection specimens that were doneat this time. Of the 631 (52.2%) Ta specimens, 218 (34.5%) were high grade, and there were 162 (13.4%) T1 specimens. In total, 506 (41.9%) specimens had muscularispropria, and 151 (39.7%) of the 380 high-risk specimens (high grade Ta, T1) had it. 85 (22.4%) of the 380 high-risk non-muscle-invasive tumors underwent re-TUR. Seven (14.6%) and one (2.7%), respectively, of the 48 T1 specimens and 37 Ta high grade specimens that went on to re-TUR had advanced to muscle-invasive illness.

For Ta high grade and T1 tumors, the rates of residual disease/early recurrence at 3–6 months were considerably higher in patients with re-TUR than in those without (56.8% vs. 82.5%; $P < 0.001$) and 39.6% vs. 84% ($P = 0.028$), respectively. Re-TUR rates are low in bladder cancer that is non-muscle invasive and at high risk. Re-TUR is necessary in this population because, in a modern series, residual cancer rates are high despite modest upstaging rates.

In a study published in **2015, Cao et al**. [68] sought to determine the impact of potential risk factors on the positive rate of bladder tumor resections performed 4-6 weeks following the initial transurethral resection procedure (TURBT) in patients with non-muscle invasive ca bladder in China. This study comprised 134 individuals with non-muscle invasive Ca bladder who had a second TURBT performed 4-6 weeks following their initial resection. Analysis was done on the existence of residual tumor and the associated risk factors, the second procedure's problems, and the variations in stage and grade between the TURBTs. Of the 134 patients, 52 had residual tumors, and 41 of them underwent upgrading, as the manuscript demonstrates.Following the review, it was concluded that patients with high grade, T1 stage, and residual tumor with multi-focality during the initial transurethral resection were at higher risk. Patients with residual tumor in Re TURBT had a considerably greater rate of progression and recurrence. In the repeated TURBT, a high incidence of residual tumor was seen. According to this study, patients with high grade, T1 stage, or multi-focality non-muscle-invasive bladder cancer should undergo repeated TURBT.

To determine the potential benefits of a second TURBT for patients with initially diagnosed T1 High-grade bladder cancer, **Jafri et al. (2015)** conducted this study.Bladder cancer (T1 high grade, non-muscle invasive) has been detected in 350 people overall. Two groups of patients were formed from this group. 150 patients in Group A had an early re-resection. 200 patients in Group B did not have an early re-resection.At the time of initial TUR, the detrusor muscle was present in 90 patients out of 150 patients (60%) in Group A and in 158 patients out of 200 patients (79%) in Group B.

Out of 350 patients, 76.67% of patients had detrusor muscles at the time of early resection. Of the individuals who had their tumors removed, 55% still had residual tumors. In Groups A and B, the total incidence of recurrence was 34.66%

and 42%, respectively. Patients not having an early re-resection during follow-up had a noticeably greater rate of tumor progression. P<0.05 for Group 14.28% vs. Group 3.85%.To obtain a full resection and identify patients that can require a radical cystectomy, a second TUR should be compulsory for all patients with T1 high grade bladder cancer.

According to **Herr et al. (2015)** [3]**,** repeat TUR improves staging accuracy, provides additional histologic material supporting accurate diagnosis, allocates appropriate therapy with improved outcomes, facilitates response to intravesical therapy, and provides important prognostic information. It also achieves optimal local control by removing residual tumors following initial TUR. Of newly diagnosed bladder tumors, 75% are non-muscle-invasive bladder cancers (NMIBCs). These include flat carcinoma in -situ and papillary cancers that are neither minimally invasive (Ta) nor minimally invasive (T1). Tumors of the papillary bladder can be categorized as high-grade (HG) or low-grade (LG).

An HG lesion called CIS is typically connected to papillary cancers. Within two to three years, NMIBCs often recur, and between five and thirty percent progress to muscle invasion. Recurrence and advancement of tumors impair quality of life, lower survival rates, and increase the burden and expense of therapy. The crucial surgical operation for the diagnosis, staging, and initial management of primary and recurrent NMIBC is transurethral resection (TUR). The goals of TUR are to remove microscopic and visible superficial and invasive tumors, as well as to give sufficient tissue for evaluating the histologic type and grade of bladder tumors and assessing the existence and depth of tumor invasion.
The results specify follow-up plans, provide guidance for additional therapy, and provide a prognosis. TUR is a common procedure that urologists are familiar with, but its outcomes are not always same because of unknown variables relating to the surgeon, the tumor, and the pathology.

The NCCN Guidelines propose a second or repeat TUR (within 6 weeks) in the following cases: incomplete TUR at first For HG tumors, large or multifocal tumors, or any T1 tumor, there is no muscle in the original material.

Bishr et al. (2014) conducted a study investigating factors influencing prognosis in patients with high-risk non-muscle-invasive Ca bladder (NMIBC) undergoing re-staging resection. This study aimed to identify candidates for early radical cystectomy. A retrospective analysis of 453 patients treated for UrothelialCa between 2006 and 2010 was performed. Of these, 94 underwent re-TUR, with 72 eligible for analysis due to non-progression to muscle-invasive disease. Re-TUR outcomes revealed residual NMIBC in 41 patients and no residual tumor (T0) in 31 patients.
Regarding tumor recurrence and progression, there was a significant difference noted between patients with pT0 and patients with residual NMIBC on re-TURBT (39% vs. 83%) (6% vs. 34%), respectively. Tumor stage on re-TURBT and the type of intravesical BCG therapy regimen (maintenance vs. induction) were found to be independent predictors of both progression-free survival (PFS) ($p = 0.008$, HR: 0.097) and recurrence-free survival (RFS) ($p = 0.001$, HR: 1.77), ($p < 0.001$ HR: 0.16), on multivariate analysis. Better RFS and PFS are linked to the existence of T0 on re-TUR, which may be a predictor of candidates for conservative therapy. Maintenance intravesical BCG therapy can improve RFS and PFS in patients with high-risk NMIBC. This study is limited by its retrospective nature and relatively small sanple size.
The results of patients having high-risk NMIBC that was primary, progressive, or recurrent were compared by **Thomas et al. (2013)[71].** In 809 individuals (average follow-up: 59 months [interquartile range: 6–190]), the study found 699 primary, 110 progressing, and 494 recurrent high-risk BCa tumors. When compared to groups with progressive (20%) and primary (14.6%) tumors, muscle invasion was more likely in recurrent

(23%) tumors (log rank p < 0.001). Compared to primary disease (19.2%; log rank p = 0.006), individuals with recurrent (25.5%) and progressive (24.6%) tumors experienced a higher rate of disease-specific death (DSM). The progressive cohort had high overall death-rate (62%) compared with recurrent (58%) and primary groups (54%; log rank p < 0.001), although other-cause mortality was equal among all groups (log rank p = 0.57). In a multivariable analysis, the tumor grouping (hazard ratio [HR]:>1.15; p < 0.026), stage (HR: >1.30; p < 0.001), patient age and sex (HR: >1.03; p < 0.037), and DSM were predictive of progression. Only in initial tumors was carcinoma in situ a reliable indicator of prognosis. Retrospective design and scant information about the usage of Bacillus Camille-Guérin are among the limitations.

Compared to primary malignancies, patients with recurrent, high-risk BCa tumors have greater rates of progression, death via suicide, and DSM. When using bladder-sparing techniques on these patients, caution should be exercised. Carcinoma in situ plays minimal predictive significance in

In order to provide data for individuals who were either not subjected to or did undergo a routine second resection, **Holmäng et al. (2013)** [8] undertook a study. In this retrospective investigation, 221 patients receiving intravesical bacillus Calmette-Guérin (BCG) treatment for newly diagnosed TaG3 or T1 bladder cancer were included.Out of 221 patients, 57 underwent a routine second resection, often known as a repeat resection (25.8%). In the first year, 0/10 patients with TaG3, 2/12 with T1G2, and 5/35 with T1G3 had progression detected. The progression rate over first year among 164 patients who didn’t undergo a second resection was 0/56 for TaG3, 1/30 for T1G2, and 8/78 for T1G3. Among the sixteen patients whose T1 tumors advanced in first year, the median age was 77.5.

Of the 164 patients, 25 TURs (25/164, 15.2%) were carried out as result of tumor found during the initial cystoscopy. Most (84/164, 51.2%) there

wasn't any recurrences throughout a 45-month median follow-up.TaG3 patients had excellent initial results, suggesting that a routine re-resection would not be necessary. Resection should be seriously considered, nevertheless, as progression was prevalent among T1 patients.

The effects of early re-resection on incidence of tumor recurrence and progression in patients having pT1 high-grade non-muscle invasive bladder cancer (HG-NMIBC) were assessed by **Vasdev et al. (2012)**. [72] Data on patient's demographics, histological parameters (such as presence of detrusor muscle at initial TUR and at re-resection), adjuvant intravesical therapy, and recurrence and progression rates were gathered retrospectively from 486 patients diagnosed with pT1 HG-NMIBC. After the first TUR, an early resection was done six weeks later. The patients were divided into two discrete groups: Group A (n = 172), who underwent an early re-resection and Group B (n = 314), which did not.61% (n = 105) of patients in Group A and 76% (n = 240) of patients in Group B had detrusor muscle during initial TUR. In 77.9% of instances, detrusor muscle was present at the time of early re-resection. Of the cases that were re-resected, 54.6% had a residual tumor. In Groups A and B, the overall incidence of tumor recurrence was 35% and 42%, respectively. Patients who didn'thave early re-resection had a considerably greater rate of cancer stage advancement during follow-up (Group B 14.4% vs. Group A 3.3%, $P < 0.05$). Accurate staging and the removal of residual illness are facilitated by early re-resection. The rates at which tumor stages advance afterward are markedly enhanced. This study suggest that every patient with HG-NMIBC should have early resection.

Gaya et al. (2012) [73] assessed rate of understaging, perioperative complications, and residual tumor in patients undergoing second transurethral resection (re-TUR) for high grade non-muscle-invasive bladder cancer.Because of lack of muscle in the first resection specimen

(cTx), twenty-two individuals had second TURs. Eight out of 47 patients (17%) had residual disease, and two cases (4.2%) had understaging; in the two patients who had understaged, the sample from the initial TUR did not contain muscularispropria. In the re-TUR, the remaining 20 cTx (90%) were cT0. In the re-TUR, they did not find any cT1 understaged (≥cT2). Twelve percent of the patients had complicationsduring second TUR: two patients needed reintervention due to bleeding, 1 patient had single febrile urinary infection, 2 patients had bladder perforations, and one patient had urethral stricture. These results demonstrated that the only single risk factor for understaging the tumor is the absence of muscle in the original resection. Thus, in these situations, the study's consideration of re-TUR is required. This study advocates that systematic re-TUR is not required and should only be considered in specific patients where complete TUR has been performed and the muscularispropria is present and tumor free (cTa-T1). This is especially true if the study believes that re-TUR is not immune to problems.

Restaging, or second transurethral resection (TUR), is necessary for the effective treatment of high-risk, non-muscle-invasive bladder cancer, according to **Herr et al. (2011)**[3] The pertinent literature describing the function of restaging TUR was reviewed in this study. Restaging TUR lowers the likelihood of early tumor recurrences, improves clinical staging, and detects more cancers than first TUR, according to cohort and randomized studies. This study suggests that bladder neoplasms that are high-risk but non-muscle invasive can be treated better with restaging TUR.

MATERIAL AND METHODS

Study-Design

A prospective-observational-research design was adopted in OUR study. It took place in a hospital that specialized in urology, ensuring a broad and diverse patient population. This study design was done by the collection of real-world data related to the management of high-grade non-muscle invasive Ca bladder (NMIBC) and provided insights into the re-resection of bladder carcinoma in routine clinical practice.

Study-Setting

The study was performed at 'The Department of Urology at Dayanand Medical College and Hospital, Ludhiana, Punjab.

Study Duration

The study was performed from October 1, 2022, to February 1, 2024

Study Population

In our study, we included patients aged >18 years, who were diagnosed with high-grade NMIBC (T1) following their initial TURBT. All participants had histopathological confirmation of high-grade urothelial carcinoma. Patients with muscle-invasive Ca bladder (T2 or higher), a prior history of bladder cancer were excluded. Additionally, patients were required to fill informed consent, ensuring that they were willing and able to participate in our study.

Inclusion Criteria

- Patients with T1 high-grade bladder cancer
- Patients aged over 18 years

Exclusion Criteria

- Multiple comorbidities
- Patients with uncorrected coagulopathy
- Patients not giving consent to participate in our study

Sample Size

The study was time-bound study.

Recruitment

Participants were enrolled from the urology department of the hospital. Eligible patients were identified after a reviewing initial TURBT histopathology results. Once identified, patients were approached and informed consent was obtained from every participants. This process made sure that participants understood the study's objectives, procedures, and potential risks, and agreed to participate voluntarily.

Intervention

Participants underwent a second TURBT within 4–6 weeks after the initial procedure, while the non-re-resection group continued with routine surveillance without additional surgery. This stratification enabled the study to compare outcomes between patients who received re-resection and those who did not, providing insights into the necessity and impact of the procedure.

Data Collection

This study included all newly diagnosed patients with space-occupying lesions in the bladder, planned for transurethral resection of bladder tumors (TURBT). After obtaining informed consent, patients underwent a comprehensive assessment, including:

- Detailed explanation of the study, disease, and management in their preferred language
- Clinical history and physical examination
- Systemic examination
- Relevant blood and urine investigations
- Radiological assessment
- Pre-anesthetic evaluation

Surgical Procedure:

TURBT was performed in the operation room under general or regional anesthesia, with obturator block used in selected cases. The procedure involved:

- Cystoscopic evaluation
- Meticulous assessment of bladder lesions, recording site, size, multiplicity, and relation to ureteric orifices
- Endoscopic, video-assisted TURBT using Karl Storz/Wolf 26 fr active cutting resectoscopes
- Resection of all visible lesions and submission for histopathological examination
- Deeper tissue resection with muscle for histopathological examination to confirm complete resection

Histopathological Examination:

- Dedicated uropathologist assessment of specimens
- Reporting of malignancy, stage, grade, and muscularispropria involvement

Second TURBT:

- Routine second TURBT performed within 4-6 weeks for pT1G3 bladder tumors
- Resection at previous scar sites and doubtful areas
- Assessment for residual or recurrent disease, with resection and histopathological examination as needed for restaging purpose.

Statistical Analysis

The collected data were described in terms of range, mean ± standard deviation, frequencies (number of cases), and relative frequencies (percentages). For discrete data, proportions were computed, and the mean and standard deviation (SD) were calculated for the continuous data. The chi-square test was applied to compare the proportions between the groups to assess statistical significance. All analyses were two-tailed, and a p-value of <0.05 was considered significant. SPSS version 21.0 was used for data analysis.

Ethical-Considerations

The institutional review boards (IRBs) of Dayanand Medical College and Hospital in Ludhiana granted ethical approval for the research. Prior to enrollment, participants were given complete details about the goals, methods, and possible dangers of the study, and their agreement was acquired. Strict secrecy was maintained on all patient data to safeguard study participants' privacy and guarantee ethical standards were followed at all times.

OBSERVATION AND RESULTS

Table 4: Age distribution of non-muscle invasive high grade bladder cancer

Age Distribution	
	No. of patients (%)
20 to 30	0 (0.00)
30 to 40	0 (0.00)
40 to 50	2 (6.7)
51 to 60	7 (23.3)
>60	21 (70.0)
Total	30 (100.0)

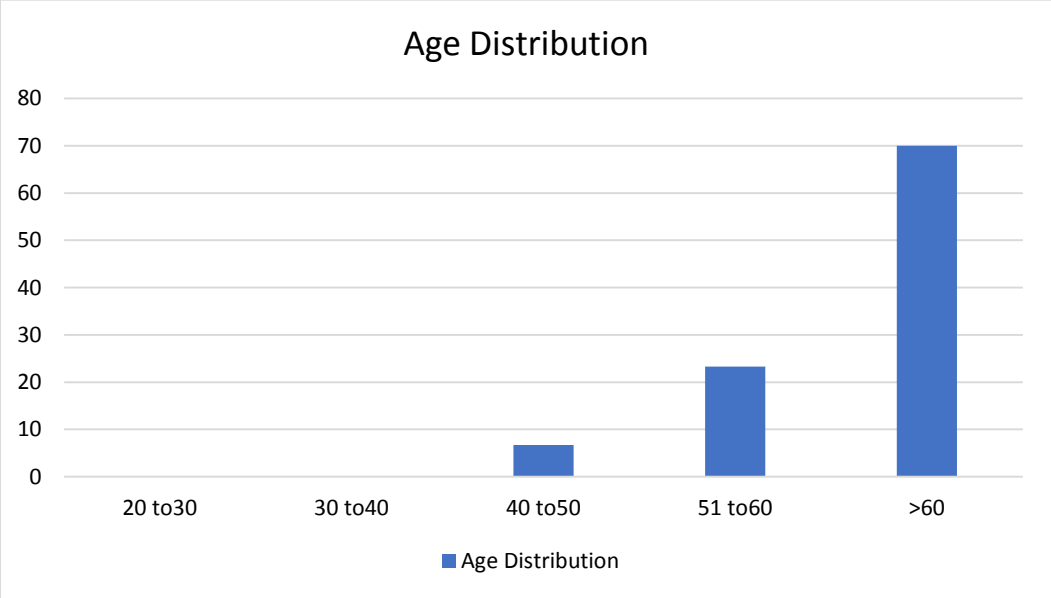

Figure 2: Age Distribution

The age wise distribution of patients shows that the majority of participants (70%) are over the age of 60, indicating that high-grade non-muscle invasive bladder cancer predominantly affects older individuals. The smallest group falls within the 40–50 age range (6.7%), while no patients are represented in the 20–40 age group, highlighting the rarity of the condition in younger populations. Mean age of was 65.5 years in our study.

Table 5: Gender distribution of non-muscle invasive high grade bladder cancer

Sex	
	No. of patients (%)
Male	29 (96.7)
Female	1 (3.3)

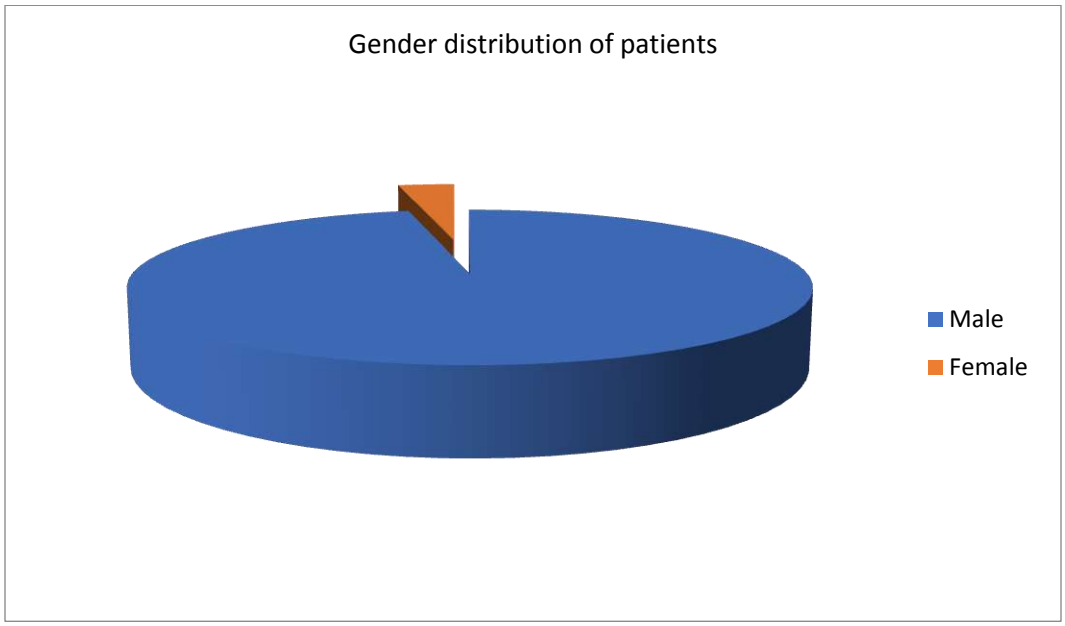

Figure 3: Gender distribution

From the above table and graph, it was observed that the gender wise distribution is highly skewed, with 96.7% of the patients being male and only 3.3% female. This suggests that non-muscle invasive bladder cancer is much more common in men than in women, reflecting the known gender disparity in bladder cancer incidence.

Table: 6 Urine Cytology in non-muscle invasive high grade bladder cancer

Urine Cytology (High Grade)	
	No. of patients (%)
High Grade	5 (16.7)
Low Grade	25 (83.3)
Total	30

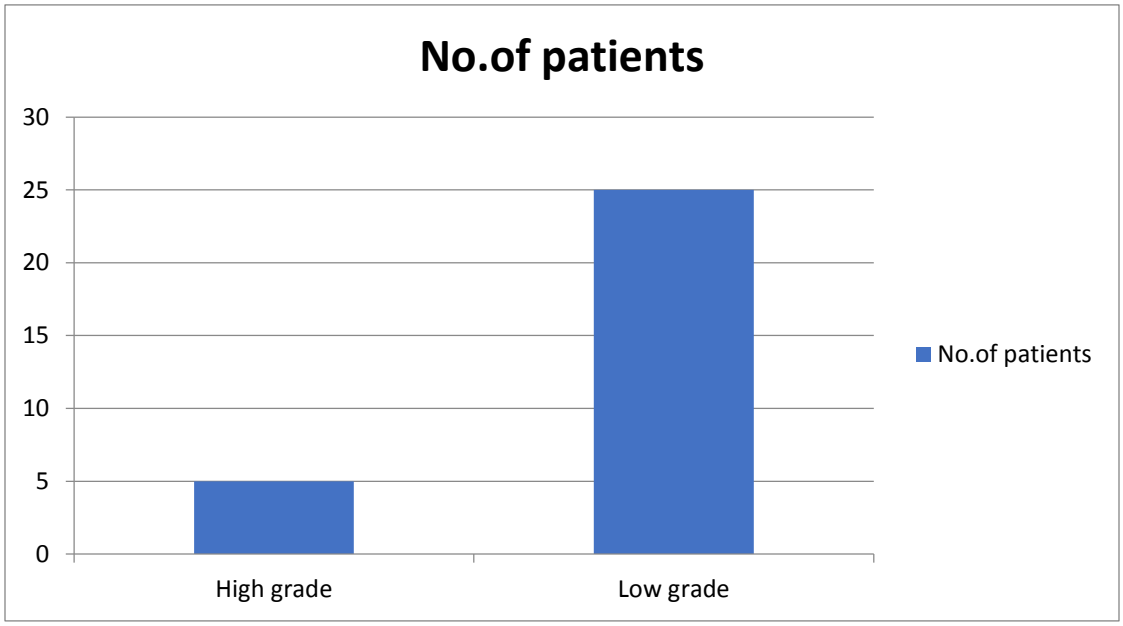

Figure 4: Urine Cytology

From the above table and graph, it was observed that 16.7% of the patients had high-grade urine cytology, while the majority, 83.3%, had low-grade cytology. This suggests that although a significant number of patients have low-grade findings, a subset is at higher risk due to the presence of high-grade cytological features.

Table 7: Association of smoking as risk factor in non-muscle invasive high grade bladder cancer

Smoking	
	No. of patients (%)
Yes	12 (40.0)
No	18 (60.0)
Total	30 (100.0)

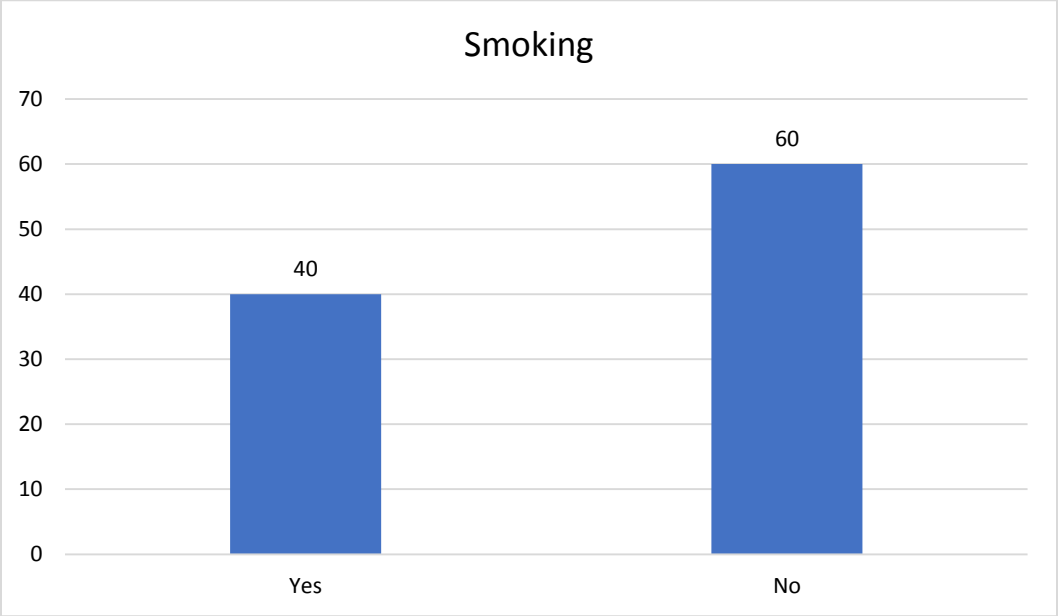

Figure 5: Association of smoking

From the above table and graph, it was observed that among the patients, 40% reported being smokers, while 60% were non-smokers. This points to smoking as a relevant but not overwhelming risk factor for bladder cancer.

Table 8: Multiplicity of primary lesion in non-muscle invasive high grade bladder cancer

Number of Lesion	
	No. of patients (%)
Single	19 (63.3)
Multiple	11 (36.7)
Total	30 (100.0)

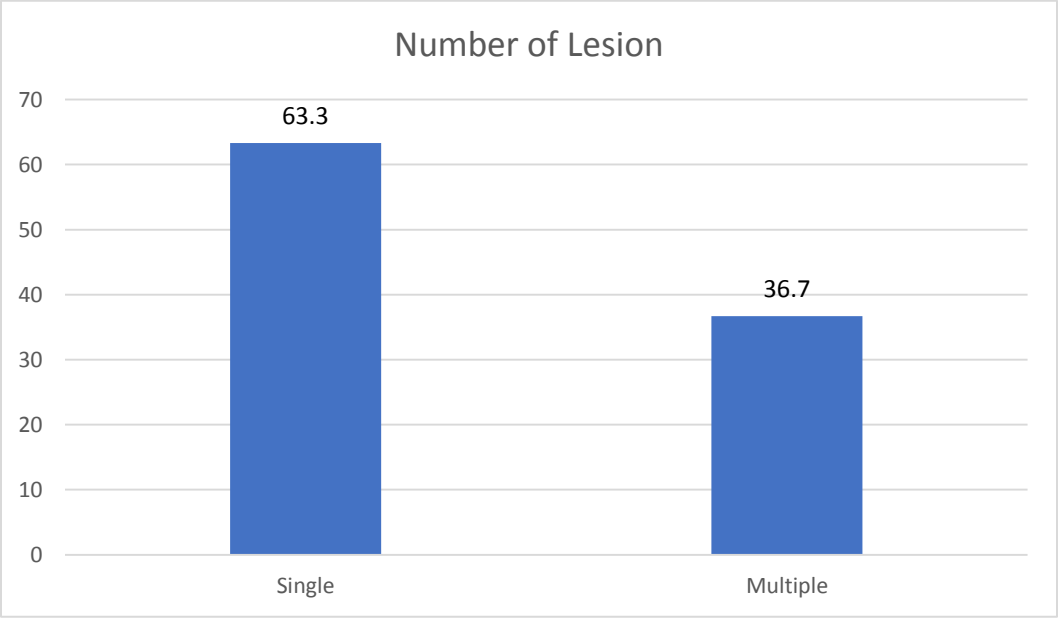

Figure 6: Multiplicity of primary lesion

From the above table and graph, it was observed that most patients (63.3%) had a single lesion, while 36.7% had multiple lesions. This distribution may reflect varying levels of disease severity, with multiple lesions potentially indicating more advanced or aggressive disease.

Table 9: Size of primary lesion in non-muscle invasive high grade bladder cancer

Size	
	No. of patients (%)
<3cm	25 (83.3)
>3cm	5 (16.7)

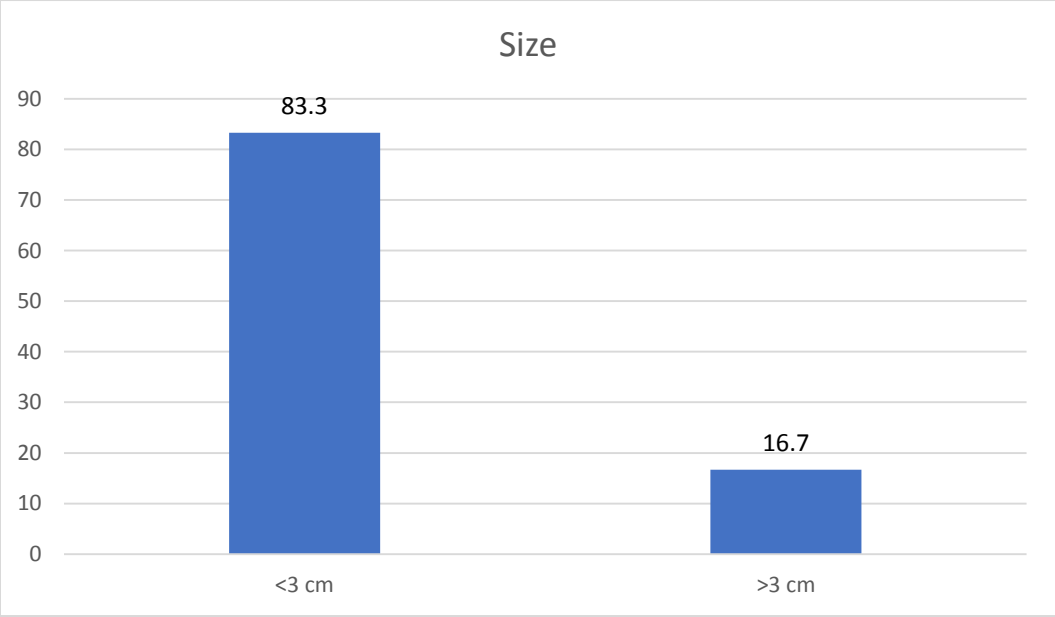

Figure 7: Size of primary lesion

From the above table and graph, it was observed that in terms of tumor size, the majority of patients (83.3%) had tumors smaller than 3 cm, while a smaller group (16.7%) had tumors larger than 3 cm. This indicates that most tumors in this cohort were small, which may change treatment outcomes and the role of re-resection in disease management.

Table 10: Location of primary lesion in non-muscle invasive high grade bladder cancer

Site	
	No. of patients (%)
Anterior wall	3 (10.0)
Posterior wall	10 (33.3)
Lateral wall	17 (56.7)
Total	30

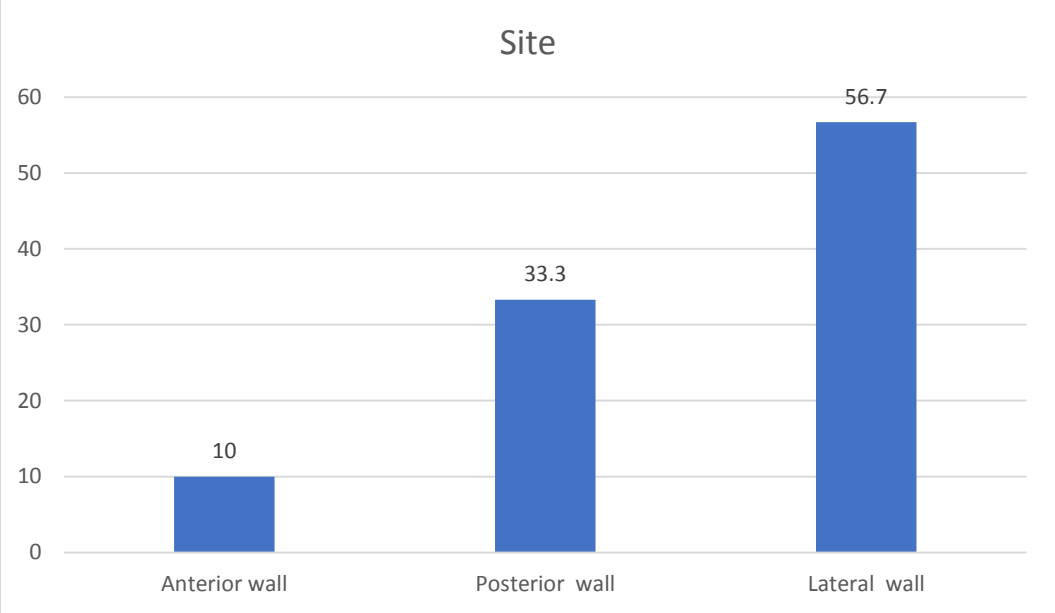

Figure 8: Location of primary lesion

The distribution of tumor site may be seen in the above table and graph, where 56.7% of tumors were found on the posterior wall, 33.3% on the lateral wall, and only 10% on the anterior wall. This indicates a tendency for tumors to develop on the posterior wall in this group of patients, which may have an impact on the surgical strategy and prognosis.

Table 11: Tumor Reoccurrence/residual tumor in re-TURBT

Tumor Reoccurrence/residual tumor in re-TURBT	
	No. of patients (%)
No Tumor	13 (43.3)
Reoccurrence /Residual Tumor	17 (56.7)
Total	30 (100.0)

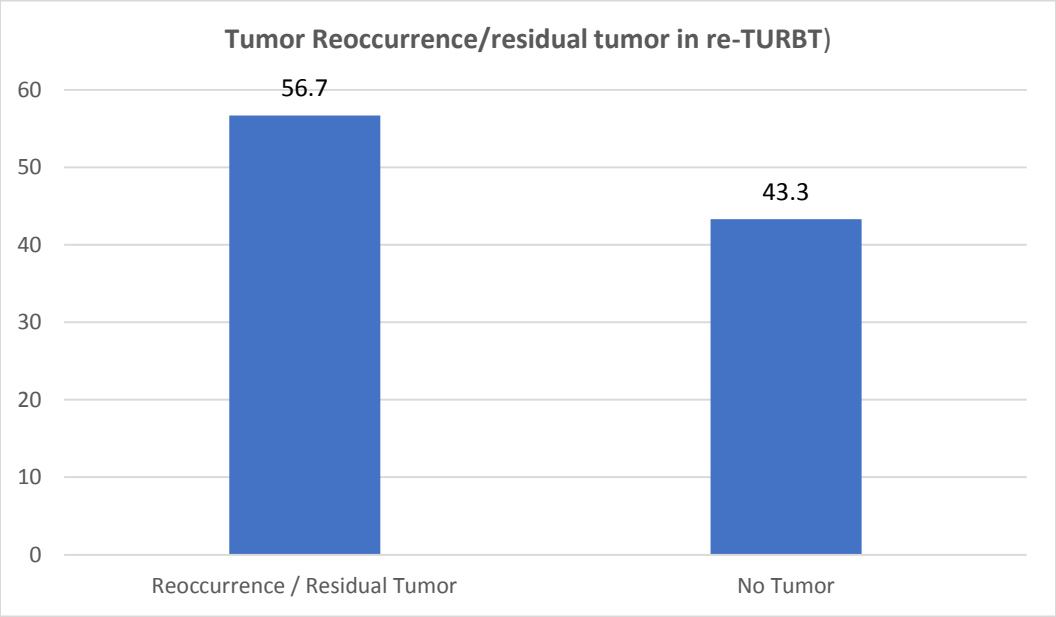

Figure 9: Tumor Reoccurrence

From the above table and graph, it was observed that 43.3% of patients didn't experienced recurrence or residual tumor following previous treatment, while 56.7% showed tumor recurrence or residual tumor. This suggests that re-resection might play an important role in reducing tumor recurrence.

Table 12: Stage of Primary tumor

Stage	
	No. of patients (%)
T1(Same Stage)	30 (100.0)

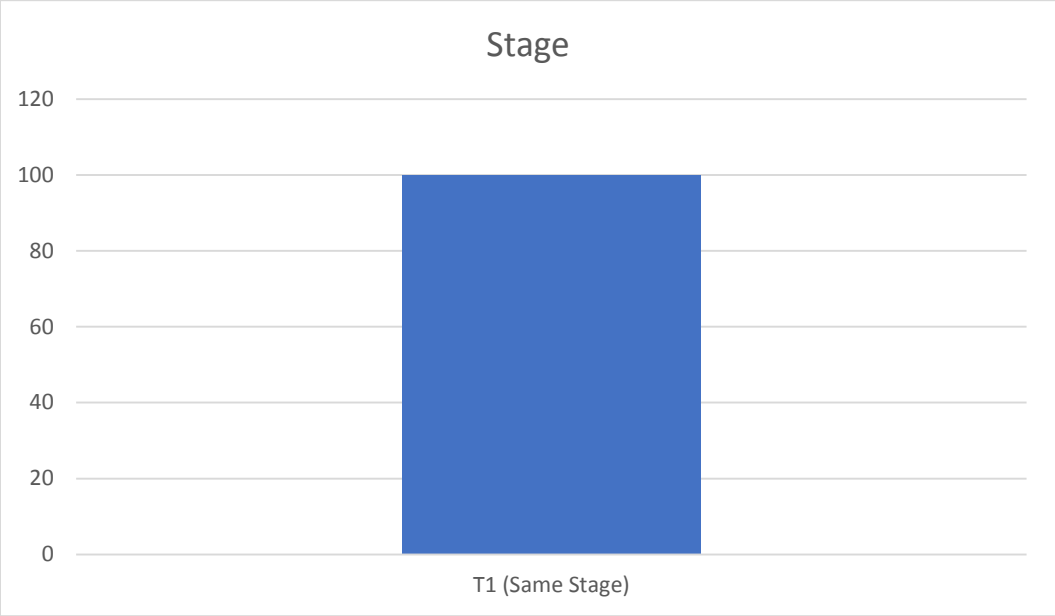

Figure 10: Stage of Primary tumor

From the above table and graph, it was observed that all patients in the study were classified as having stage T1 tumors (100%), indicating that despite re-resection, the tumor stage remained consistent across the cohort.

Table 13: The presence of muscle in primary TURBT and its correlation with re-TURBT findings

	Muscle Present	Muscle Not Present
Tumor	7	10
No Tumor	5	8

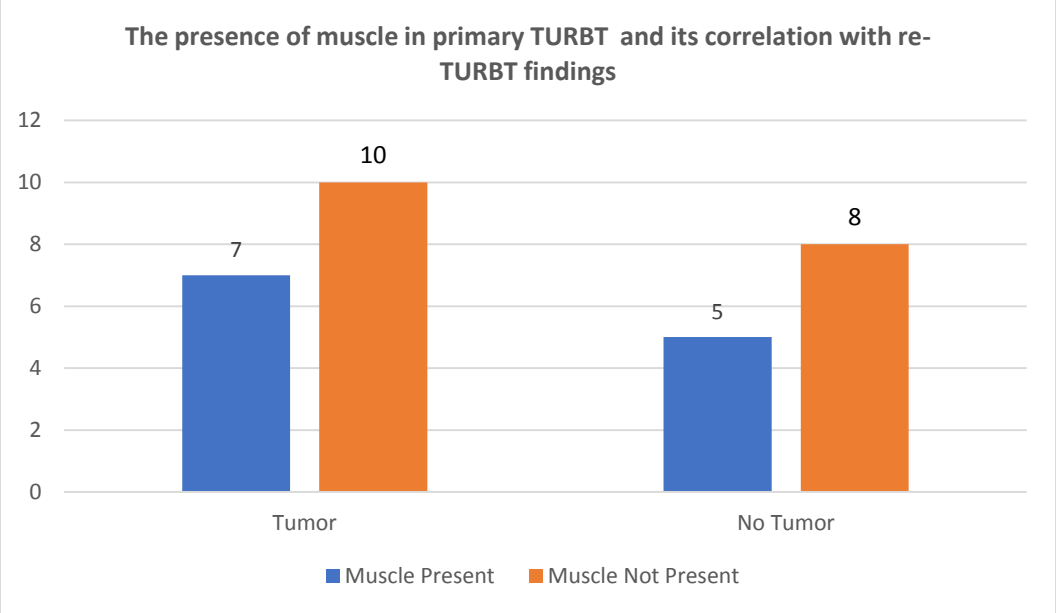

Figure 11: The presence of muscle in primary TURBT and its correlation with re-TURBT findings

Above tables and figure shows the comparison of the presence of muscle vs the absence of muscle in primary TURBT with the reoccurrence of tumor. This study shows that out of 12 patients with muscle present in specimen in primary TURBT , 7 patients experienced residual/ recurrent tumor on re-TURBT, while 5 patients didn't. On other hand, out of 18 patients with muscle absent in primary TURBT, 10 patients experienced reoccurrence/ residual tumor on re-TURBT.

Table 14: Size of tumor in primary TURBT and its correlation with re-TURBT findings

Tumor	Size	
	<3cm	>3cm
Tumor	13	4
NoTumor	12	1

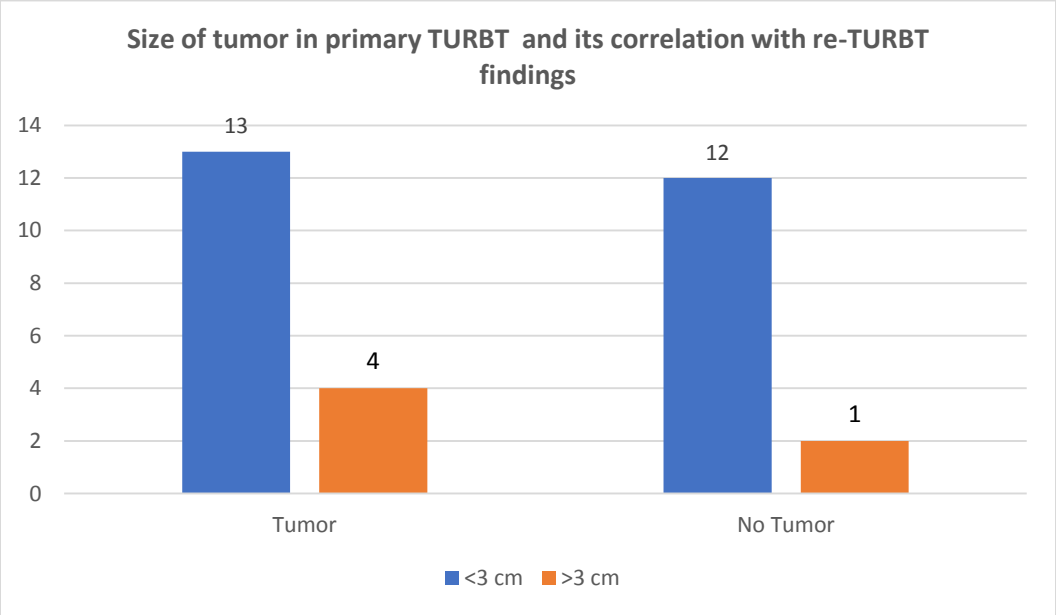

Figure 12: Size of tumor in primary TURBT and its correlation with re-TURBT findings

It was noticed from the above table and graph that, out of the patients who presented with tumor recurrence, 4 had tumor sizes more than 3 cm and 13 had tumor sizes smaller than 3 cm. Twelve of the patients without tumor recurrence in re TURBT had tumors smaller than 3 cm, and only one had tumors larger than 3 cm.

Table 15: Number of tumor in primary TURBT and its correlation with re-TURBT findings

Tumor	Number of Lesion	
	Single	Multiple
Tumor	10	7
NoTumor	9	4

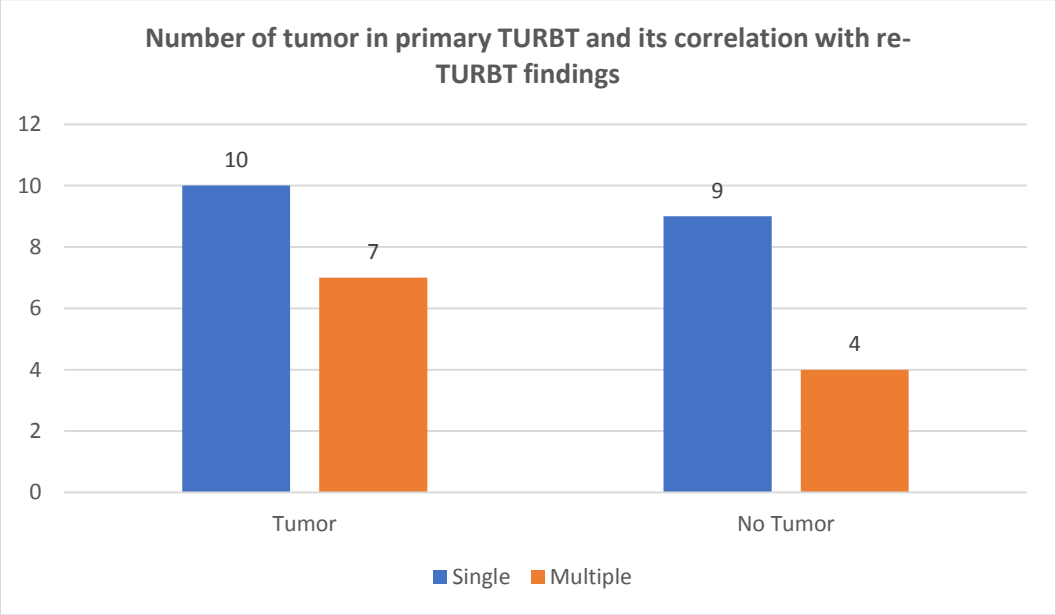

Figure 13: Number of tumor in primary TURBT and its correlation with re-TURBT findings

It was noted from the above table and graph that 7 patients with multiple lesions and 10 patients with a single lesion experienced tumor recurrence. Additionally, the study showed that only four individuals with multiple lesions and nine individuals with a single lesion had no tumor recurrence. Given that 7 out of the 11 patients with multiple lesions experienced tumor recurrence, the data suggests that patients with multiple lesions are more likely to experience residual tumor or tumor recurrence. On the other hand, patients with a single lesion had a higher likelihood of no tumor recurrence (9 out of 19).

Table 16: Location of tumor in primary TURBT and its correlation with re-TURBT findings

	Anterior wall	Posterior wall	Lateral wall
Tumor	3	8	6
No Tumor	0	2	11

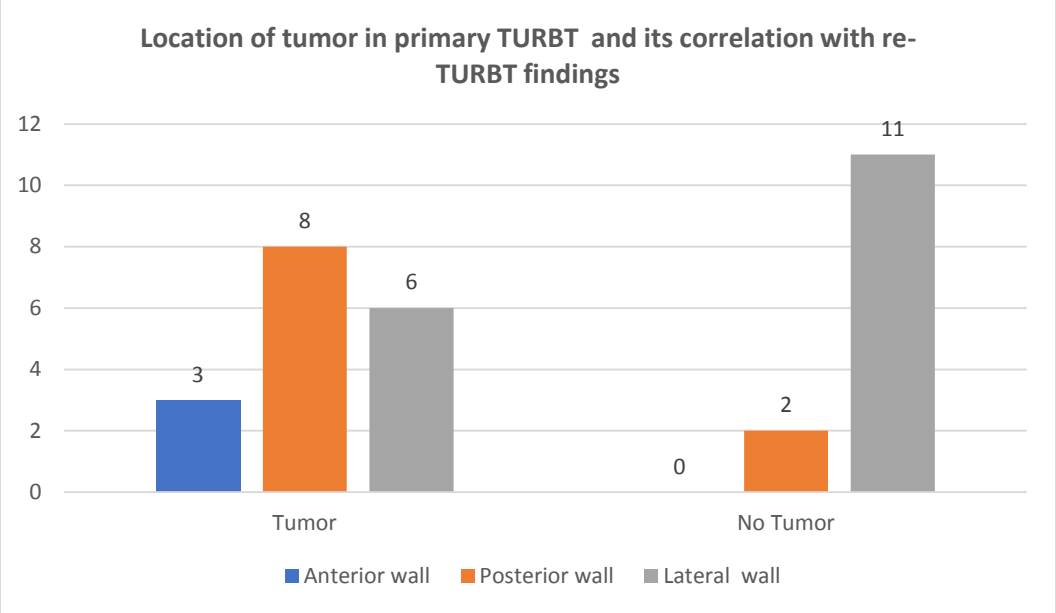

Figure 14: Location of tumor in primary TURBT and its correlation with re-TURBT findings

From the above table and graph, it was discovered that all three patients with tumors on the anterior wall had tumor recurrence. Eight of the ten patients with posterior wall tumors had tumor recurrence, while only two did not, according to the study. Last but not least, out of the 17 patients whose tumors were situated on the lateral wall, only 6 had tumor recurrence, while the remaining 11 did not. These results imply that cancers on the anterior and posterior walls are more likely to recur, with recurrence occurring in almost all cases of tumors on the anterior wall. However, tumors on the lateral wall seem to have a decreased chance of coming back, as most patients report

Table 17: Re-staging after reTURBT

Stage in re-TURBT	
Under Stage	5
Same Stage	23
Upstage	2

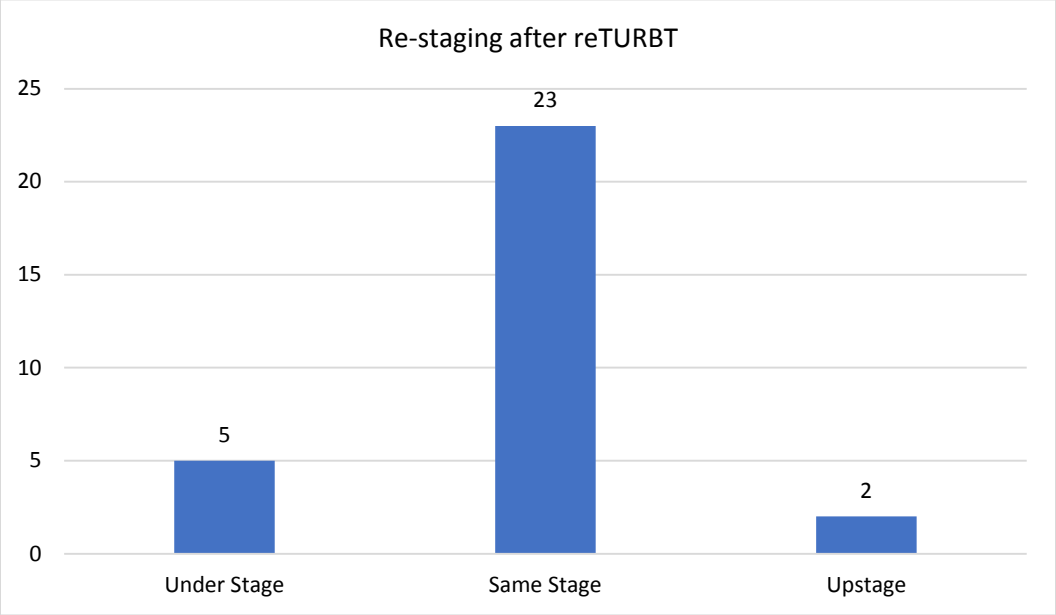

Figure 15: Re-staging after reTURBT

From the above table and graph, it was observed that 5 patients showed a downstaging of their tumor in re-TURBT, indicating a less aggressive form of the disease after re-resection. The majority of patients (23) remained at the same stage, meaning that re-TURBT did not reveal a change in the tumor's severity or progression. While 2 patients were upstaged after re-TURBT, indicating a more aggressive or advanced form of the disease that may have been missed during the initial TURBT. This suggests that re-TURBT is essential in accurately assessing the true extent of the disease, as it can detect both downgrading and upgrading of the tumor stage.

DISCUSSION

The present study has aimed to explore role of re-resection in high grade non-muscle invasive bladder cancer. The study was performed on 30 patients. A prospective-observational-research design was adopted in this study to assess the objectives of the study. This section has discussed major findings with reference studies.

Demographic Distribution:

Our study found that more than half of patients (70%) were over 60 years old, demonstrating that this form of bladder cancer predominantly affects older individuals. No patients were observed in the 20–40 age range, indicating that high-grade bladder cancer is rare in younger populations.

In line with observatonsof our study Vasdev et al., (2012)[72] reported that the mean age of patients diagnosed with pT1 HG-NMIBC was 73.63 ± 9.2 years. In a study Soria et al., (2023)[62] reported that median age of the patients was 74 (66–80) years. These findings were consistent with the findings of our study. In our study, mean age was 65.5 years, which was significantly lower than previously described studies.

The study found out that a striking gender disparity in our study, with 96.7% of patients being male. This finding is consistent with existing knowledge that, bladder cancer is far more prevalent in men than in women.

In similarity to our study, Vasdev et al., (2012)[72] reported a majority of male patients in their study i.e., 77.8% male and 22.2% female patients. Soria et al., (2023)[62] also reported a majority of male patients (83.33%) while the number of female patients was only 5 out of 30 patients (16.77%).

In a study by Desai et al., (2024)[61]majority of the patients belonged to the age range of 50–60 years. The results signified that the study population predominantly consisted of the male population (84.8%).

Risk Factors

As a risk factor for Ca bladder, smoking was reported by 40% of patients in our study. Sixty percent of patients did not smoke, which implies that along with smoking, other variables also play a vital role in the onset of the condition. This is consistent with study done by Freedman et al in 2011. [12] where Smoking is considered the most important risk factor and is assumed to account for close to 50%. The second commonest risk factor is occupational exposure to amines, polycyclic hydrocarbons, and chlorine containing hydrocarbons as used in paint, dye, metal, and petroleum industries. In other study by Burger et al., (2013) [13] described risk factors were genetic predisposition, environmental pollution, prior medical conditions, and socio-economic parameters. Soria et al., (2023)[62] in their study, they reported that, there were a majority of patients with smoking habits (83.33%). This supports the finding of our study that smoking may contribute to the development of bladder cancer.

Urine cytology

Understanding the relationship between urine cytology and tumor grading is pivotal in the clinical assessment and management of urological malignancies. In our study involving 30 patients, we observed a notable finding: only 5 patients (approximately 16.7%) demonstrated high-grade cytology. This raises significant considerations regarding the efficacy and limitations of urine cytology as a diagnostic tool. A greater risk of persistent or recurrent disease was seen in patients with high-grade histology, positive urine for malignant cytology, tumour size >3 cm, presence of perivesical fat stranding, and upper tract alterations (Desai et al., 2024)[61]

Tumor size

The size of the primary lesion is also a useful prognosticating factor in these lesions. Many studies have proved a lesion <3cm will have decreased chances of recurrence and progression and this in included in the EAU guidelines of non muscle invasive bladder tumor. In our study, out of 30 patients, 25 patients (83.3%) had a<3cm primary lesion, and only 5 patients had >3 cm lision in primary TURBT. Because smaller tumours are typically easier to control, especially in context of re-resection, it is possible that favourable treatment outcomes in most cases are influenced by the smaller tumour size. Previous studies have demonstrated a positive relation between tumour size and the likelihood of disease recurrence, specifically identifying tumours greater than 3 cm as a significant predictor of persistent or recurrent disease (Desai et al., 2024) [61]

Tumor number

Multifocality of the primary lesions is a poor prognostic factor in TCC. In our study, out of 30 patients, majority of patients had single lesion in primary specimen that is, 19 patients (63.3%) while only 11 patients (36.3 %) had multiple lesions. In a study by Ferro et al.in (2022) [63], Re-TURB high-grade, multifocality, and lympho-vascular invasion were a predictors of poor BCG therapy response. Patients who didn’trespond to BCG reported worse oncological outcomes.

Tumor location

These findings highlight the importance of considering site of tumor in bladder cancer. The location of tumor can influence treatment options, prognosis, and overall patient management. For example, tumors located in the anterior wall may be more difficult to resect surgically than tumors located in the lateral or posterior wall so, reoccurence is noted more common in anterior wall. Our study suggests that the lateral wall of the bladder is the most common site of tumor, with 56.7% of patients in this

study. The posterior wall was the second most common site, with 33.3% of patients, while the anterior wall was the least common site, with only 10% of patients.

Tumor architecture

Tumor architecture, papillary or sessile, size of the lesion and site of lesion are most important prognostic factors for recurrence of the disease. A solitary papillary lesion is considered as a good prognostic factor as against multiple sessile lesions. In our study, most of the patients had single growth (63.3%) with growth size less than 3 cm (83.3%). Among the 19 patients with solitary lesions, 10(52.7%) had tumor positive in the second resection while patients with multiple tumors7 (63.63%) were having tumor reoccurence in the second resection. 4 out of 5 (80%) of the >3cm lesions were having reoccurence of tumor in the second resection. Perhaps this is the subgroup, solitary papillary lesions and <3cm in size, that are least likely to benefit from re-TURBT. Sessile lesions and > 3 cm lesions had significant positivity in the re-TURBT. The chances of tumor positivity in the re-TURBT in sessile group are high and are statistically significant when compared to solitary papillary lesions. In this study, data highlights that all 3 patients with tumors located on the anterior wall experienced tumor recurrence, suggesting that, anterior wall location of tumor might be associated with a elevated risk of reoccurrence, whereas, significant majority (8 out of 10) of patients with posterior wall tumors experienced tumor recurrence. While a majority (11 out of 17) of patients with tumors in the lateral wall did not experience recurrence, a small number (6 out of 17) did, suggesting that this site may have an intermediate risk for recurrence. This further emphasizes the importance of considering the site of the primary tumor in predicting recurrence.

Muscle in specimen

It was formerly conveyed that the absence of muscle layer in the resected specimen is an implication of clinical understaging. Also, undervaluation of the depth of cancer invasion is an important error, especially when a muscle-invasive lesion is present. Additionally, Dutta et al.[21] reported a 64% rate of understaging in T1 tumors if muscularispropria was absent in the specimen versus 30% if it was present. In our study, we can make out that, out of 30 patients, muscle was not present in 18(60%) of patients and tumor reoccurence was noted in 7 of the 12 patient having muscle in primary TUR specimen. Whereas 10 out of 18 patients who don't have muscle in their specimen shows reoccurence. In a study by Gontero et al. (2016)[7] ,re-resected patients showed increased overall, cancer-specific, recurrence-free, and progression-free survival analysis, but only if detrusor muscle was sufficiently sampled during initial TURBT.

Recurrence and Residual Tumor:

High-quality evidence on the oncological role of reTUR is urgently needed. Although reTUR is recommended for all T1 tumors and for patients with absence of muscle in their initial TUR specimen (with the exception of LG Ta disease) (Babjuk et al., 2022).[6]

Our study found that, a measurable proportion of patients (56.7%) experienced recurrence or residual tumor after previous treatment, highlighting the importance of re-resection in managing bladder cancer and reducing the risk of recurrence. All patients staged as T1 in primary TURBT, 5 patients showed a downstaging of their tumor after re-TURBT, indicating a less aggressive form of the disease after re-resection. The majority of patients (23) remained at the same stage. Although in a study, the presence of pT1 disease at reTUR has been considered a strong predictor of adverse long-term oncological outcomes, with 25–70%

of patients experiencing progression within 5 yr, depending on the series (Palou et al., 2012[24]; Herr et al., 2006)[3].

The primary endpoint of our study was to assess the impact of re-resection on cancer detection rates and accurate re-staging. The rate of residual tumour after initial TUR varies widely in published literature, ranging from 4% to 78% (Divrik et al., 2006[5]; Herr et al., 2006)[3]. In line with findings of our study, Vasdev et al., (2012)[72] reported that,residual tumour were identified at re-resection in 54.6% (94/172) of patients. Soria et al., (2023)[62] in their study reported that, out of 30 patients (15 each arm) disease recurrence was noted in three patients (23%) in the reTUR arm and six patients (40%) in the upfront BCG arm. In another study Desai et al., (2024)[61] reported that of 250 patients (deep muscle involvement, n = 237 and no muscle involvement, n = 13) 18% of patients had residual or recurrent tumors.

Re-TURBT Outcomes:

TURBT is the standard of treatment for the management of NMIBC. According to protocol and guidelines, restage TURBT in high-risk cases should be done to check whether there is a recurrence, residual disease, or proliferation (Babjuk et al., 2013).[6]In a recent systematic review findings suggest that,, the mean probability of upstaging to MIBC at the time of reTUR was approximately 8%. However, the probability was ≤3% in 11 series and 0% in two studies, highlighting high variability between centers and emphasizing the importance of experienced and dedicated surgeons and the quality of the first TUR. (Cumberbatch et al., 2018)[29].

In our study it was noted that after re-TURBT, 5 patients were down-staged, indicating a less aggressive disease course, while 2 patients were upstaged, reflecting a more advanced stage that may have not looked upon during initial resection. Re-TURBT proved essential for accurately staging the disease and guiding further treatment.

In a study Soria et al., (2023)[62] reported that at reTUR, persistent disease was found in four patients (29%) and upstaging to muscle-invasive disease in one (7%). Similarly, Vasdev et al., (2012)[72] revealed that 19/94 tumors was found to be up-graded when compared to original histology, representing a rate of up-grading of 20.2%. 2 patients were upstaged after re-TURBT, indicating a more aggressive or advanced form of the disease that may have been missed during the initial TURBT.

Overall, the findings from this study highlights the importance of factors such as age, gender, tumor size, multiplicity of lesions, tumor location, and morphology in determining bladder cancer recurrence and progression. Re-resection plays a vital role in accurately assessing tumor stage, managing residual disease, and potentially downstaging aggressive tumors, offering better long-term outcomes.

SUMMARY AND CONCLUSION

SUMMARY

The present prospective observational was performed on 30 patients to justify the role of re-resection in high grade non-muscle invasive Ca bladder. The summary of the major findings of the study are as follows:

- The majority of patients (70%) are over the age of 60, indicating that high-grade non-muscle invasive Ca bladder predominantly affects older individuals.
- The gender distribution is heavily skewed, with 96.7% male and only 3.3% female, showing that bladder cancer is much more common in men.
- Most patients (83.3%) had low-grade urine cytology, while 16.7% had high-grade cytology, indicating a subset at higher risk because of the presence of high-grade features.
- Smoking was a relevant but not overwhelming risk factor, with 40% of patients being smokers.
- 63.3% of patients had a single lesion, while 36.7% had multiple lesions, which may reflect varying disease severity.
- Tumor size distribution shows that 83.3% had tumors smaller than 3 cm, and 16.7% had tumors larger than 3 cm, with smaller tumors being more common.
- Tumors were located predominantly on the posterior wall (56.7%), followed by the lateral wall (33.3%), and the anterior wall (10%).
- 56.7% of patients experienced recurrence or residual tumor after treatment, while 43.3% showed no recurrence, highlighting the role of re-resection.
- Tumor size distribution revealed that smaller tumors (<3 cm) were more common in both patients with and without tumor recurrence.

- Patients with multiple lesions have a higher likelihood of recurrence, as 7 out of 11 with multiple lesions experienced tumor recurrence.
- Tumors located on the anterior and lateral walls were more prone to recurrence, while tumors on the posterior wall showed a lower likelihood of recurrence.
- Sessile tumors were more common overall, especially in larger tumors (>3 cm), while papillary tumors were found exclusively in smaller tumors (<3 cm).
- All patients were having stage T1 tumors, with 16.6% upstaging, 6.6% downstaging and 76.6% showing no stage changes after re-resection, confirming the importance of re-resection in assessing tumor progression.

CONCLUSION

This prospective-observational-study highlights the critical role of re-resection in the management of high-grade non-muscle invasive Ca bladder. The findings indicate that re-resection is instrumental in accurately assessing the stage of the disease, identifying residual or recurrent tumors, and determining the true extent of the tumor. The study also shows that variables such as age, gender, tumor size, number of lesions, tumor location, and morphology significantly impact recurrence risk.

Re-resection was shown to downstage the tumor in some patients, potentially altering the way of treatment by revealing a less aggressive type of the disease. Conversely, upstaging in a little subset of patients underscores the value of re-resection in detecting more advanced carcinome that may have been missed during initial resection. The data also suggest that individuals with multiple lesions and tumors located on the anterior or lateral walls are at a high risk of recurrence, emphasizing the need for vigilant follow-up and potentially more aggressive interventions in these cases.

In conclusion, re-resection remains a vital tool in the effective management of high-grade non-muscle invasive bladder cancer, improving diagnostic accuracy and enhancing treatment outcomes. Its routine use should be considered to minimize the recurrence risk and ensure proper treatment strategies are employed.

BIBLIOGRAPHY

1. NiederAM, Brausi M, Lamm D, O'Donnell M, Tomita K, Woo H, et al. Management of stage T1 tumors of the bladder: International Consensus Panel. Urology 2005;66:108-25.
2. KirkaliZ, Chan T, Manoharan M, Algaba F, Busch C, Cheng L, et al. Bladder cancer: Epidemiology, staging and grading, and diagnosis. Urology 2005;66:4-34.
3. Herr HW, Donat SM. A re-staging transurethral resection predicts early progression of superficial bladder cancer. *BJU Int.* 2006;97:1194–8.
4. Lamm D, Persad R, Brausi M, Buckley R, Witjes JA, Palou J, et al. Defining progression in nonmuscle invasive bladder cancer: It is time for a new, standard definition. J Urol 2014;191:20-7.
5. DivrikRT, Yildirim U, Zorlu F, Ozen H. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesicalmitomycin: a prospective, randomized clinical trial. J Urol 2006;175:1641–4.
6. Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez EscrigJL,et al. European Association of Urology guidelines on non–muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ). EurUrol 2022;81:75–94.
7. Gontero P, Sylvester R, Pisano F, Joniau S, Oderda M, Serretta V, et al. The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of in a large multicentre cohort of patients with T1 high-grade/grade 3 bladder cancer treated with bacilleCalmette-Guérin. BJU Int 2016;118:44–52.
8. Holmäng S. High-grade non-muscle-invasive bladder cancer: is reresection necessary in all patients before intravesical bacillus Calmette-Guérin treatment? Scand J Urol 2013;47:363–9.

9. Culpan M, Kazan O, Acar HC, Iplikci A, Atis G, YildirimA.The probability of residual tumor detection in the second transurethral resection of pT1 urothelial bladder cancer according to the risk factors. ActasUrolEsp 2022;46:423–30.
10. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
11. Cancer Care Ontario. Ontario Cancer Statistics 2018. Toronto, Ontario: Cancer Care Ontario; 2018.
12. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA. 2011;306:737–45.
13. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63:234–41.
14. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours. Eur Urol. 2016;70:106–19.
15. Dahm P, Gschwend JE. Malignant non-urothelial neoplasms of the urinary bladder: a review. Eur Urol. 2003;44:672–81.
16. Mostofi F, Sobin L, Torloni H. Histological typing of urinary bladder tumours. Geneva, Switzerland: World Health Organization; 1973.
17. Soukup V, Capoun O, Cohen D, Hernandez V, Babjuk M, Burger M, et al. Prognostic Performance and Reproducibility of the 1973 and 2004/2016 World Health Organization Grading Classification Systems in Non-muscle-invasive Bladder Cancer: A European Association of Urology Non-muscle Invasive Bladder Cancer Guidelines Panel Systematic Review. Eur Urol. 2017;72:801–13.

18. Moch H, Humphrey P, Ulbright T, Reuter V. WHO classification of tumours of the urinary system and male genital organs. Lyon, France: World Health Organization; 2016.
19. Edge SB, Compton CC. The American JointCommittee on Cancer: the 7th edition of theAJCC cancer staging manual and the future of TNM. Ann SurgOncol. 2010;17:1471-74.
20. Kaseb H, Leslie S, Soon-Sutton T, Aeddula N. Bladder cancer. StatPearls.2024 Jun 8.
21. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancerstatistics, 2023. CA Cancer J Clin. 2023;73:17-48.
22. Kamat AM, Hahn NM, Efstathiou JA, Lerner SP, Malmström P-U, Choi W, et al.. Bladder cancer. *Lancet* (2016) 388:2796–810.
23. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al.. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71:209–49.
24. Palou J, Sylvester RJ, Faba OR, Parada R, Peña JA, Algaba F, et al. Femalegender and carcinoma in situ in the prostaticurethra are prognostic factors for recurrence,progression, and disease-specific mortality int1g3 bladder cancer patients treated with bacilluscalmette-guerin. Eur Urol. 2012;62:118-25.
25. Leblanc B, Duclos AJ, Benard F, Côté J, Valiquette L, Paquin JM, et al. Long-termfollowup of initial ta grade 1 transitional cellcarcinoma of the bladder. J Urol.1999;162:1946-50.
26. Shariat SF, Sfakianos JP, Droller MJ, Karakiewicz PI, Meryn S, Bochner BH. The effect of age and gender on bladder cancer: a critical review of the literature. *BJU Int* (2010) 105:300–8.
27. Schultzel M, Saltzstein SL, Downs TM, Shimasaki S, Sanders C, Sadler GR. Late age (85 years or older) peak incidence of bladder cancer. *J Urol* (2008) 179:1302–1305; discussion 1305-1306.

28. DobruchJ, Daneshmand S, Fisch M, Lotan Y, Noon AP, Resnick MJ, et al.. Gender and bladder cancer: a collaborative review of etiology, biology, and outcomes. *EurUrol* 2016;69:300–10.
29. Cumberbatch MGK, Foerster B, Catto JWF, Kamat AM, Kassouf W, Jubber I, et al. Repeat transurethral resection in non–muscle-invasive bladder cancer: a systematic review. EurUrol 2018;73:925–33.
30. SafiriS, Kolahi A-A, Naghavi M, Global Burden of Disease Bladder Cancer Collaborators. Global, regional and national burden of bladder cancer and its attributable risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *BMJ Glob Health* (2021) 6:e004128.
31. Yan H, Ying Y, Xie H, Li J, Wang X, He L, et al.. Secondhand smoking increases bladder cancer risk in nonsmoking population: a meta-analysis. *Cancer Manag Res* 2018;10:3781–91.
32. Kwan ML, Haque R, Young-Wolff KC, Lee VS, Roh JM, Ergas IJ, et al. Smoking behaviors and prognosis in patients with non-muscle-invasive bladder cancer in the be-well study. *JAMA Netw Open* 2022;5:2244430.
33. Zuniga KB, Graff RE, Feiger DB, Meng MV, Porten SP, Kenfield SA. Lifestyle and non-muscle invasive bladder cancer recurrence, progression, and mortality: available research and future directions. *Bladder Cancer* 2020;6:9–23.
34. Westhoff E, Wu X, Kiemeney LA, Lerner SP, Ye Y, Huang M, et al. Dietary patterns and risk of recurrence and progression in non-muscle-invasive bladder cancer. *Int J Cancer* 2018;142:1797–804.
35. Leeming RC, Karagas MR, Gilbert-Diamond D, Emond JA, Zens MS, Schned AR, et al.. Diet quality and survival in a population-based bladder cancer study. *Nutr Cancer* 2022;74:2400–11.

36. Catto JWF, Rogers Z, Downing A, Mason SJ, Jubber I, Bottomley S, et al.. Lifestyle factors in patients with bladder cancer: a contemporary picture of tobacco smoking, electronic cigarette use, body mass index, and levels of physical activity. *EurUrol Focus* .2023;9:974-82.
37. Zhang W, Yang F, Mao S, Wang R, Chen H, Ran Y, et al.. Bladder cancer-associated microbiota: recent advances and future perspectives. *Heliyon* 2023;9:13012.
38. Daneshmand S, Schuckman AK, Bochner BH, et al. Hexaminolevulinate blue-light cystoscopy in non-muscle-invasive bladder cancer: review of the clinical evidence and consensus statement on appropriate use in the USA. *Nat Rev Urol.* 2014;11:589–96.
39. Chou R, Gore JL, Buckley D, Fu R, Gustafson K, Griffin JC, et al. Urinary biomarkers for diagnosis of bladder cancer: a systematic review and meta-analysis. *Ann Intern Med.* 2015;163:922–31.
40. Sylvester RJ, Oosterlinck W, Holmang S, Sydes MR, Birtle A, Gudjonsson S, et al. Systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy after transurethral resection with transurethral resection alone in patients with stage pTa-pT1 urothelial carcinoma of the bladder: which patients benefit from the instillation? *EurUrol* 2016;69:231–44.
41. Shelley MD, Court JB, Kynaston H, et al. Intravesical bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. *Cochrane Database Syst Rev.* 2003;2003:CD003231.
42. Fernandez-Gomez J, Madero R, Solsona E, Unda M, Martinez-Piñeiro L, Gonzalez M, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. *J Urol.* 2009;182:2195–2203.

43. Musat MG, Kwon CS, Masters E, Sikirica S, Pijush DB, Forsythe A. Treatment outcomes of high-risk non-muscle invasive bladder cancer (HR-NMIBC) in real-world evidence (RWE) studies: systematic literature review (SLR). *Clin Outcomes Res* 2022;14:35–48.
44. Matulay JT, Li R, Hensley PJ, Brooks NA, Narayan VM, Grossman HB, et al.. Contemporary outcomes of patients with nonmuscle-invasive bladder cancer treated with bacillus calmette-guérin: implications for clinical trial design. *J Urol* (2021) 205:1612–21.
.45. Williams SB, Howard LE, Foster ML, Klaassen Z, Sieluk J, De Hoedt AM, et al.. Estimated costs and long-term outcomes of patients with high-risk non–muscle-invasive bladder cancer treated with bacillus calmette-guérin in the veterans affairs health system. *JAMA Netw Open* 2021;4:213800.
46. Seo M, Langabeer JR, II. Demographic and survivorship disparities in non–muscle-invasive bladder cancer in the united states. *J Prev Med Pub Health* 2018;51:242–7.
47. Wang EYH, Pihlström N, Malmström P-U, Gårdmark T. Improved long-term outcome of patients with non-muscle invasive, low and intermediate risk bladder cancer between 1997 and 2014; a Swedish population-based study. *Scand J Urol* 2022;56:221–6.
48. Maisch P, Retz M, Gschwend JE, Koll F, Schmid SC. Clinical practice guidelines for bladder cancer: a systematic review and meta-analysis using the AGREE II instrument. *UrolInt* 2021;105:31–40.
49.Heer R, Lewis R, Duncan A, Penegar S, Vadiveloo T, Clark E, et al.. Photodynamic versus white-light-guided resection of first-diagnosis non-muscle-invasive bladder cancer: PHOTO RCT. *Health Technol Assess* 2022;26:1–144.
50. Stenzl A, Rouprêt M, Witjes JA, Gontero P. High-quality transurethral resection of bladder tumour needs additional forms of tumour delineation. *EurUrol* 2023;83:193–4.

51. Tabayoyong WB, Kamat AM, O'Donnell MA, McKiernan JM, Ray-Zack MD, Palou J, et al.. Systematic review on the utilization of maintenance intravesical chemotherapy in the management of non-muscle-invasive bladder cancer. *EurUrol Focus* 2018;4:512–21.

52. TaylorJ, Becher E, Steinberg GD. Update on the guideline of guidelines: non-muscle-invasive bladder cancer. *BJU Int* 2020;125:197–205.

53. McElree IM, Steinberg RL, Martin AC, Richards J, Mott SL, Gellhaus PT, et al.. Sequential intravesical gemcitabine and docetaxel for bacillus calmette-guérin-naïve high-risk nonmuscle-invasive bladder cancer. *J Urol* 2022;208:589–99.

54. Zhao H, Chan VW-S, Castellani D, Chan EO-T, Ong WLK, Peng Q, et al. Intravesicalchemohyperthermia vs. bacillus calmette-guerin instillation for intermediate- and high-risk non-muscle invasive bladder cancer: a systematic review and meta-analysis. *Front Surg* 2021;8:775527.

55. Regnier S, Califano G, Elalouf V, Albisinni S, Aziz A, Di Trapani E, et al.Restaging transurethral resection in Ta high-grade nonmuscle invasive bladder cancer: a systematic review. *CurrOpinUrol* 2022;32:54–60.

56. Gendy R, Delprado W, Brenner P, Brooks A, Coombes G, Cozzi P, et al. Repeat transurethral resection for non-muscle-invasive bladder cancer: a contemporary series. BJU international. 2016;117:54-9

57. Gotto GT, Shea-Budgell MA, Ruether JD. Low compliance with guidelines for restaging in high-grade T1 bladder cancer and the potential impact on patient outcomes in the province of Alberta. Can Urol Assoc J. 2016;10:33–38.

58. Patschan O, Holmang S, Hosseini A, Jancke G, Liedberg F, Ljungberg B, et al. Second-look resection for primary stage T1 bladder cancer: a population-based study. Scand J Urol. 2017;51:301–7.

59. Gordon PC, Thomas F, Noon AP, Rosario DJ, Catto JW. Long-term outcomes from re-resection for high-risk non–muscle-invasive bladder cancer: a potential to rationalize use. European Urology Focus. 2019;5:650-7.
60. Eroglu A, Ekin RG, Koc G, Divrik RT. The prognostic value of routine second transurethral resection in patients with newly diagnosed stage pT1 non-muscleinvasive bladder cancer: results from randomized 10-year extension trial. Int J ClinOncol. 2020;25:698–704.
61. Desai D, Gupta A, Sharma U, Goel H, Katiyar V, Mehra K. Role of restage transurethral resection of bladder tumor in high-risk non-muscle invasive bladder cancer. National Journal of Physiology, Pharmacy and Pharmacology. 2024;14:353.
62. Soria F, Rosazza M, Livoti S, Dutto D, Colucci F, Sylvester RJ, et al. Repeat transurethral resection (TUR)+ bacillus Calmette-Guérin (BCG) versus upfront induction BCG after TUR in high-risk non–muscle-invasive bladder cancer: feasibility phase of a randomized controlled study. European Urology Focus.2023.; 236-5.
63. Ferro M, Barone B, Crocetto F, Lucarelli G, Busetto GM, Del Giudice F, et al. Predictive clinico-pathological factors to identify BCG, unresponsive patients, after re-resection for T1 high grade non-muscle invasive bladder cancer. InUrologic Oncology: Seminars and Original Investigations 2022; 40:490.e13-490.e20.
63. Hu H, Zhou M, Yang B, Zhou S, Liu Z, Zhang J. A systematic review on the role of repeat transurethral resection after initial en bloc resection for non-muscle invasive bladder cancer.Journal of Clinical Medicine. 2022;11:5049.
64. Demir DO, Doluoglu OG, Yildiz AK, Kacan T, Veli M, Demirbas A, et al. Effect of Re-TUR time on recurrence and progression in high-risk non-muscle-invasive bladder cancer. Cirugía y cirujanos. 2022;90:6-12.
65. Paciotti M, Casale P, Colombo P, Fasulo V, Saita A, Lughezzani G, et al. Long-term follow-up after en bloc transurethral resection of non–

muscle-invasive bladder cancer: Results from a single-center experience. European Urology Open Science. 2021;26:64-71.

66. NaselliA, Hurle R, Paparella S, Buffi NM, Lughezzani G, Lista G, Casale P, Saita A, Lazzeri M, Guazzoni G. Role of restaging transurethral resection for T1 non–muscle invasive bladder cancer: a systematic review and meta-analysis. European urology focus. 2018;4:558-67.

67. Tae BS, Jeong CW, Kwak C, Kim HH, Moon KC, Ku JH. Pathology in repeated transurethral resection of a bladder tumor as a risk factor for prognosis of high-risk non-muscle-invasive bladder cancer.PloS one. 2017;12:189354.

68. Minardi D, Milanese G, Parri G, Lacetera V, Muzzonigro G. Non-muscle invasive high grade urothelial carcinoma of the bladder. Which factors can influence understaging at the time of radical cystectomy?.ArchivioItaliano di Urologia e Andrologia. 2016;88:13-6.

69. Cao M, Yang G, Pan J, Sun J, Chen Q, Chen Y, Chen H, Xue W. Repeated transurethral resection for non-muscle invasive bladder cancer. International Journal of Clinical and Experimental Medicine. 2015;8:1416.

70. Bishr M, Lattouf JB, Latour M, Saad F. Tumour stage on re-staging transurethral resection predicts recurrence and progression-free survival of patients with high-risk non-muscle invasive bladder cancer. Canadian Urological Association Journal. 2014;8:306.

71. Thomas F, Noon AP, Rubin N, Goepel JR, Catto JW. Comparative outcomes of primary, recurrent, and progressive high-risk non–muscle-invasive bladder cancer.European urology. 2013;63:145-54.

72. VasdevN, Dominguez-Escrig J, Paez E, Johnson MI, Durkan GC, Thorpe AC. The impact of early re-resection in patients with pT1 high-grade non-muscle invasive bladder cancer.Ecancermedicalscience. 2012;6.

73. Gaya JM, Palou J, Cosentino M, Patino D, Rodríguez-Faba O, Villavicencio H. A second transurethral resection could be not necessary in all high grade non-muscle-invasive bladder tumors. ActasUrológicasEspañolas (English Edition). 2012;36:539-44.
74. Jafri SS, Niazi ZI, Akhtar MS. The Clinical Value of Immediate Second Transurethral Resection in Patients with High Grade Non-Muscle Inasive Bladder Cancer (HG-NMIBC).Annals of Punjab Medical College. 2015;9:174-9.

PROFORMA

Name:

Age: **Sex:** M / F

Chief Complaints: X months

O / E:

Creatinine: mg**%.**
Cytology:

Radiology: USG:

IVU:

CECT:

Radiology Staging:

Past History: smoking yes/no

Procedure Details
Date:

No. of lesions: single/ Multiple

Size:<3 cm / > 3 cm

SIGNATURE OF CANDIDATE SIGNATURE OF SUPERVISOR

Site:

Bladder neck / Dome

Posterior wall / Anterior wall

Left lat wall / Right lat wall

Assosiated lesions:

Appearance: Invasive / Non invasive Bimanually

Complications:

Biopsy: CIS / Ta / T1 / T2 / T3 / T4

PUNLMP / Low Grade / High Grade

G1 / G2 / G3

Muscle in specimen:

Re TURBT for STAGING

Procedure: Re TURT (for staging)
Date:

Previous scars: Recurrence: Y / N

No. of lesions: single / Multiple

Size:<3 cm / > 3 cm

Site:

Bladder neck / Dome

Posterior wall / Anterior wall

Left lat wall / Right lat wall

Re resection from:

Distance from orifice:

Associated lesions:

Appearance: Invasive / Non invasive

Complications:

Biopsy: No tumor Same stage/grade

Up stage

Down stage

Previous: CIS / Ta / T1 / T2 / T3 / T4

PUNLMP / Low Grde /HIgh Grde

Now : : CIS / Ta / T1 / T2 / T3 / T4

PUNLMP / Low Grde /High Grde

SIGNATURE OF CANDIDATE SIGNATURE OF SUPERVISOR

S. NO.	Patient characteristics				INVESTIGATIONS			Smoking (yes/no)	Procedure details			
	Name	age	sex	MRD No.	High grade (Y/N)	USG KUB	CECT KUB		Date	Number of lesion	size	Site
1	HS	68	M	1574392	N		enhancing mass like thickening along right posterelateral wall	N	10-11-2022	Single	<3 cm	right posterolateral wall
2	MLS	72	M	1489982	N	Two lesions in left anterolateral wall of bladder	Two echogenic projections in left lateral wall of bladder	Y	04-04-2023	multiple	<3 cm	left anterolateral wall
3	AKS	64	M	1482956	Y	Assymetrical wall thickening along lest lateral wall and base	mass from left posterior and lateral wall extending to left vuj	y	27-03-2023	multiple	<3 cm	left posterior and lateral wall
4	KK	76	M	1678694	N	Polypoidal lesion at right posteriolateral wall		N	04-02-2023	Single	<3 cm	right posterolateral wall
5	BS	70	M	278372	N	Sessile bladder growth at left lateral wall	enhancing mass like thickening along left posterelateral wall	N	03-06-2022	single	<3 cm	left posterolateral wall
6	PS	58	M	1449282	Y	Polypoidal lesion with peripheral calcification at left posteriolateral wall		N	28-05-2022	Single	<3 cm	left posterolateral wall
7	GC	58	M	1696679	N	No e/o any bladder growth	wall thickening along left posterolateral wall	y	18-11-2022	single	<3 cm	left posterolateral wall
8	VK	45	M	1395294	N	polipoidal lesion at right posterolateral wall		y	22-02-2023	single	<3 cm	right posterolateral wall
9	SS	65	M	1540074	N	Echogenic mass 15x 2 mm in right posterolateral wall of UB with right hydroureteronephrosis		Y	03-06-2023	Single	<3 cm	right posterolateral wall
10	LR	73	M	1534881	N	Multiple bladder growth 4.5x 4.5 cm	hereogenously enhancing polipoidal soft tissue mass at right posterolatral wall of UB	Y	15-Jun	multiple	>3 cm	right posterolateral wall
11	RS	92	M	1426411	N	Assymetrical wall thickening along left lateral wall and base		N	20-11-2022	multiple	<3 cm	Left lateral wall
12	BS	56	M	931256	N	ECHIGENIC MASS LISION 1.5X 2.4 CM INVOLVING RIGHT VUJ		Y	03-06-2023	multiple	<3 cm	right posterolateral wall
13	KR	48	M	1196837	N	FOCAL NODULAR MASS ALONG RIGHT LATERAL WALL OF UB MEASURING 3.5X1 CM	PLAQUE LIKE THICKENING WITH INVOLVEMENT OF RIGHT VUJ 4.7X1.5 CM	Y	01-08-2023	Single	>3 cm	right posterolateral wall
14	RL	57	M	1426411	N		MULTIPLE POLYPOIDAL MASS 4.2X 1CM	N	09-09-2023	multiple	>3 cm	RIGHT LATERAL WALL, BASE , LEFT LATERAL WALL
15	CS	68	M	1588292	Y		IRREGULAR POLYPOIDAL MASS ALONG LEFT POSTERPLATERAL WALL OF UB WITH INVOLVEMENT OF LEFT VUJ	N	13-09-2023	Single	<3 cm	LEFT POSTEROLATERAL WALL AND BASE
16	RR	62	M	1586326	N	POLYPOIDAL MASS ALONG RIGHT LATERAL WALL OF UB INVOLVING RIGHT VUJ	MULTIFOCAL SESSILE LISION INVOLVING RIGHT POSTEROLATERAL WALLWITH INVOLVEMENT OF RIGHT VUJ	N	11-09-2023	multiple	<3 cm	RIGHT LATERAL WALL, DOME
17	SRH	78	M	1395802	N	THICKENED BLADDER WALL WITH LEFT BLADDER WALL LISION		N	15-09-2023	Single	<3 cm	ANTERIOR WALL OF BLADDER

S. NO.			Biopsy			Re-TURBT					
	Associated lesions	Complications	Stage	Grade	Muscle in specimen	Date	Previous scar reoccurence	Number of lesions	Size	Site	Biopsy
1	none	none	T1	high grade	not involved	05-01-2023	yes	single	<3 cm	right posterolateral wall	areas of coagulative necrosis
2	none	hyponatremia	T1	high grade	not included in biopsy	12-05-2023	yes	single	<3 cm	left anterolateral wall	high grade with no infiltration in muscularis propria
3	none	none	T1	high grade	not included in biopsy	22-04-2023	no	multiple	>3 cm	left posterior wall	high grade with infiltration to muscularis propria
4	none	bladder clot formation	T1	high grade	not included in biopsy	13-03-2023	no	none			high grade with no infiltration in muscularis propria
5	none	none	T1	high grade	not included in biopsy	15-04-2023	yes	single	<3 cm	left posterolateral wall	low grade non invasive
6	none	none	T1	high grade	not included in biopsy	15-04-2023	no	none			low grade non invasive
7	none	none	T1	high grade	not included in biopsy	28-03-2023	yes	single	>3 cm	left posterolateral wall	low grade non invasive
8	none	dysuria	T1	high grade	not included in biopsy	31-03-2023	yes	single	<3 cm	right posterolateral wall	high grade with no infiltration in muscularis propria
9	lision at bladder neck, trigone, and base	none	T1	high grade	not included in biopsy	15-07-2023	no	none			high grade with no infiltration in muscularis propria
10	Multiple lisions at trigone	none	T1	high grade	not included in biopsy	22-07-2024	yes	multiple	<3 cm	right posterolateral wall	high grade with no infiltration in muscularis propria
11	none	none	T1	high grade	not involved	10-01-2023	YES	SINGLE	<3cm	left lateral wall	high grade non invasive
12	b/l VUJ can not be seen	none	T1	high grade	not involved	13-08-2023	yes	SINGLE	<3 cm	right posterolateral wall	high grade with infiltration to muscularis propria
13	RIGHT VUJ INVOLVED	none	T1	high grade	not included in biopsy	15-09-2023	no	none			high grade with no infiltration in muscularis propria
14	INVOLVEMENT OF PROSTATIC URETHRA AND BLADDER NECK	none	T1	high grade	not involved	07-10-2023	YES	multiple	>3 cm	RIGHT LATERAL WALL, BASE , LEFT LATERAL WALL	high grade with no infiltration in muscularis propria
15	INVOLVEMENT OF LEFT VUJ	none	T1	high grade	not involved	19-11-2023	yes	SINGLE	<3 cm	left posterolateral wall	high grade with no infiltration in muscularis propria
16	RIGHT VUJ INVOLVED	none	T1	high grade	not included in biopsy	26-11-2023	no	none			high grade with no infiltration in muscularis propria
17		bladder clot formation	T1	high grade	not included in biopsy	11-12-2023	yes	Single	<3cm	right posterolateral wall	high grade non invasive

S. NO.	Patient characteristics				INVESTIGATIONS			Smoking (yes/no)	Procedure details			
	Name	age	sex	MRD No.	High grade (Y/N)	USG KUB	CECT KUB		Date	Number of lesion	size	Site
18	SC	58	M	643751	N	BLADDER GROWRH 9X7 MM AT RIGHT POSTEROLATERAL WALL OF BLADDER		N	11-10-2023	Single	<3 cm	right posterolateral wall
19	BS	65	M	1743731	Y	AN ECHOGENIC LESION 10X20 MM AT BASE OF BLADDER		Y	12-06-2024	Single	<3 cm	BASE
20	JS	76	M	1751633	N	LARGE ILL DEFINED UB MASS ALONG LEFT POSTEROLATERAL WALL OF UB	POLYPOIDAL LISION ON POSTEROLATERAL WALL OF UB	Y	19-06-2024	Single	>3 cm	left posterolateral wall
21	KL	72	M	1738203	N	Sessile bladder growth at left lateral wall	FEW SOL SEEN ARRISING FROM LEFT POSTEROLATERAL WALL OF UB	N	05-06-2024	multiple	<3 cm	Left lateral wall
22	BS	68	M	1749880	N		MILD WALL THICKENING OF UB ALONG POSTERIOR WALL	N	15-06-2024	SINGLE	<3 cm	POSTERIOR WALL OF UB
23	RK	63	M	1749759	N		A POLYPOIDAL MASS 1.8X1.8 CM AT RIGHT LATERAL WALL OF UB	N	13-Jun	Single	<3 cm	right posterolateral wall
24	GS	66	M	1647023	N		A POLYPOIDAL MASS 1.6X2.9 CM AT RIGHT LATERAL WALL OF UB	N	13-06-2024	Single	<3 cm	right posterolateral wall
25	AS	72	M	1647569	N	1.7X 1.7 CM POLYPOIDAL THICKENING AT RIGHT LATERAL WALL OF UB		Y	31-01-2024	MULTIPLE	<3 cm	BASE, RIGHT LATERAL WALL REACHING UPTO PROSTATIC URETHRA
26	A	72	M	1664633	N	Two lesions in right anterolateral wall of bladder 19x 19 mm and 38x 20 mm	MULTIPLE POLYPOIDAL MASSAT PASTEROLATERAL WALL AND RIGHT LATERAL WALL OF UB	N	05-02-2024	multiple	<3 cm	RIGHT LATERAL WALL
27	SS	54	F	1485559	N	BLADDER GROWRH 9X7 MM AT LEFT POSTEROLATERAL WALL OF BLADDER		N	12-03-2024	multiple	<3 cm	LEFT LATERAL WALL
28	RL	72	M	1696696	Y	IRREGULAR WALL THICKENING AT ANTERIOR AND SUPERIOR WALL 19X 17 MM		Y	22-03-2024	Single	<3 cm	left anterolateral wall
29	AA	53	M	1683623	N	LARGE ILL DEFINED UB MASS ALONG LEFT POSTEROLATERAL WALL OF UB	5.2X 2.8 CM GROWTH AT LEFT LATERAL WALL OF U.B	N	01-03-2024	Single	>3 cm	Left lateral wall
30	D	65	M	1645620	N	BLADDER GROWRH 9X7 MM AT LEFT POSTEROLATERAL WALL OF BLADDER		N	06-04-2024	Single	<3 cm	Left lateral wall

S. NO.			Biopsy			Re-TURBT					
	Associated lesions	Complications	Stage	Grade	Muscle in specimen	Date	Previous scar reoccurence	Number of lesions	Size	Site	Biopsy
18	none	none	T1	high grade	not involved	21-12-2023	yes	SINGLE	<3 cm	right posterolateral wall	high grade with no infiltration in muscularis propria
19	none	none	T1	high grade	not included in biopsy	19-07-2024	yes	single	<3 cm	BASE	high grade with no infiltration in muscularis propria
20	NONE	bladder clot formation	T1	high grade	not included in biopsy	19-07-2024	yes	single	<3 cm	left posterolateral wall	high grade with no infiltration in muscularis propria
21	REACHING UPTO BLADDER NECK	none	T1	high grade	not included in biopsy	18-06-2024	yes	multiple	>3 cm	left lateral wall	high grade with no infiltration in muscularis propria
22	none	none	T1	high grade	not involved	21-07-2024	no	none			high grade with no infiltration in muscularis propria
23	none	none	T1	high grade	not involved	16-07-2024	no	NONE			high grade non invasive
24	none	none	T1	high grade	not included in biopsy	14-07-2024	no	none			high grade with no infiltration in muscularis propria
25	BULBAR STRICTURE PRESENT ,	NONE	T1	high grade	not involved	04-03-2024	no	none			high grade non invasive
26	none	none	T1	high grade	not included in biopsy	09-03-2024	yes	SINGLE	<3 cm	right anterolateral wall	high grade with no infiltration in muscularis propria
27	none	none	T1	high grade	not included in biopsy	16-04-2024	none	none			high grade with no infiltration in muscularis propria
28	none	none	T1	high grade	not involved	15-05-2024	none	none			low grade non invasive
29	none	none	T1	high grade	not involved	04-05-2024	yes	SINGLE	>3 cm	left lateral wall	high grade with no infiltration in muscularis propria
30	none	none	T1	high grade	not involved	09-05-2024	none	none			high grade with no infiltration in muscularis propria

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No. BFUHS/2K23p-TH/ 81 **Date** 01/01/24

The Principal
Dayanand Medical College & Hospital
Ludhiana

Subject:: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 25.09.2023 has approved the plan of thesis of **Nikhil Chauhan**, a student of your college for **MCh Urology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
To determine the role of reresection in high grade non-invasive bladder cancer. .

Supervisor	**Co-Supervisor:-**	**Co-Supervisor:-**
Dr. Arvind Goyal	Dr. Harmandeep Singh Chahal	Dr. Aminder Singh
Assoc. Prof.,	Asstt. Professor	Assoc. Professor
Dept. of Urology	Dept. of Urology	Dept. of Pathology

The student may submit the thesis in triplicate alongwith the plan in triplicate also, to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She may be directed to attach a photocopy of this letter with the forwarding letter while submitting thesis in the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic, if any.

Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*

TO DETERMINE THE ROLE OF RERESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MCh

IN

UROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES
FARIDKOT

OCTOBER, 2022

DR. NIKHIL CHAUHAN

DEPARTMENT OF UROLOGY
DAYANAND MEDICAL COLLEGE &HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	TO DETERMINE THE ROLE OF RERESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER
For the degree of	MCh Urology
Name of the candidate	Dr. Nikhil Chauhan
Supervisor	Dr. Arvind Goyal, Associate Professor, Department of Urology, DMCH, Ludhiana
Co-supervisors	Dr. Harmandeep Singh Chahal, Assistant Professor, Department of Urology, DMCH, Ludhiana. Dr. Aminder Singh, Associate Professor, Department of Pathology, DMCH, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: transurethral resection of bladder tumor (TUR) is considered the gold standard for the management of non-muscle invasive bladder cancer (NMIBC), followed by adjuvant intravesical therapy according to risk stratification. A repeat TUR (reTUR) is now considered an essential step to obtain complete tumor resection and appropriate staging in T1 stage disease. Most national and international guidelines recommend reTUR, mainly due to high prevalence of residual tumor found after reTUR and its clinical implications. Nevertheless, controversy on the topic still exists as some argued that reTUR may not be needed when an adequate first TUR has been performed.

Aim of Study: The primary aim of this study is to assess the clinical value of reTURBT in patients stratified by clinical indications. The secondary aim of the study is to compare the safety of TURBT and reTURBT.

Materials & Methods: The study will be conducted among the patients admitted to Department of Urology, Dayanand Medical College and Hospital, Ludhiana from 21st November, 2022. The study design is a prospective observational study. Information shall be collected through a pre- designed performa for each patient chosen to be a part of the study with detailed history, clinical examination and complete investigational workup. Details of the study will be explained to each case. Analysis will be done with the collected details. A pre-informed consent from each patient shall be taken.

Clinical Significance: Transurethral resection of bladder tumor (TURBT) aims at completely resecting all the visible tumors, whenever feasible. This provides histological staging and grading to classify tumors as nonmuscle invasive or muscle invasive. The treatment and outcomes of these two histopathological stages are entirely different. However, in certain situations such as high-grade superficial disease, there is a possibility of inadequate/improper staging of the tumor.

Keywords: Non invasive bladder cancer, TURBT, Re TURBT, Safety.

(Signature) Candidate	(Signature) Supervisor	(Signature) Co-supervisor	(Signature) Co-supervisor	(Signature) Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"TO DETERMINE THE ROLE OF RERESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER"** exist in the Department of Urology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself/herself under our supervision and guidance.

Supervisor

Dr. Arvind Goyal
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Dr. Sandeep Sharma
Professor & Head
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Place: Ludhiana

Date: 10/12/22

APPROVAL PROFORMA
BYRESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. Nikhil Chauhan
Department	MCh Urology
Topic of Thesis	A STUDY TO DETRMINE ROLE OF RERESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER
Likely date of appearing in PG examination	MAY, 2024
Date of enrollment	30.04.2022
Name of Head of Department	Dr. Sandeep Sharma
1) Supervisor **2) Co-Supervisor**	Dr. Arvind Goyal Dr. Harmandeep Singh Chahal Dr. Aminder Singh
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Harpreet Kaur (Professor & Head, Pathology)	Mr. R K Sharma (Legal Expert)
Dr. Jaspal Singh (Professor & Head, Surgery)	Dr. Ramit Mahajan (Associate Professor, Gastroenterology)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
Dr. Sandeep Kaushal (Dean Academics & Professor & Head, Pharmacology)	Dr. Sandeep Kaushal (Dean Academics & Professor & Head, Pharmacology)
Dr. Gurpreet S Wander (Vice Principal)	Dr. Gurpreet S Wander (Vice Principal & Professor & Head, Cardiology)
	Dr. Gagandeep Singh (Secretary, Ethics Committee Professor & Head, Neurology)

Approved: Yes / ~~No~~

Dr. Sandeep Puri
Chairperson
Research Committee
Chairperson
Research Committee

Approved: (Yes) / No

Prof. Arvind Malhotra
Chairperson
Ethics Committee
Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	DR. NIKHIL CHAUHAN LAKSHAY HOSPITAL, MANNUPURAM COLONY , NEAR ST. MARYS SCHOOL, BIJNOR , U.P.
2	NAME OF THE INSTITUTE	DAYANAND MEDICAL COLLEGE AND HOSPITAL, LUDHIANA
3	COURSE OF STUDY AND SUBJECT	M.Ch UROLOGY
4	DATE OF ADMISSION OF COURSE	30st April 2022.
5	TITLE OF THE TOPIC	TO DETERMINE THE ROLE OF RERESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER

6. BRIEF RESUME OF THE INTENDED WORK

6.1NEED FOR THE STUDY

Transurethral resection of bladder tumor (TURBT) aims at completely resecting all the visible tumors, whenever feasible. This provides histological staging and grading to classify tumors as nonmuscle invasive or muscle invasive. The treatment and outcomes of these two histopathological stages are entirely different. However, in certain situations such as high-grade superficial disease, there is a possibility of inadequate/improper staging of the tumor. Persistent disease after resection has been observed in 33%–55% of the patients with T1 tumors and in about 41.4% of those with Ta high-grade tumors.[1-5] This is true even if detrusor muscle was included but not invaded at the initial TURBT especially if the histopathology was high grade T1. The likelihood of upstaging to T2 at second resection of an initially T1 tumor ranges from 4% to 25%, and increases to 45% if no muscle was seen in the initial resection specimen.[6] Hence, both the European Association of Urology (EAU) and American Urological Association guidelines recommend restage TURBT in all T1 as well as all high-grade tumors. The problem of restage TURBT are logistics, cost of repeat surgery and the complications associated with TURBT, such as bladder perforation and stricture. Moreover, restage may not be performed in the stipulated time because of lack of OR slot availability in public hospitals or poor compliance of patients. As the symptoms resolve, some patients tend to ignore advice or become hesitant to undergo second surgery within a short span. These patients either avoid the surgery or are lost to follow-up. These problems may be further compounded by resource constraints, typical to a tertiary care setup in India. Hence, there is a need to strongly rationalize the role of restage TURBT in resource constraint setup and to identify the tumor characteristics which can guide the requirement/exemption for restage TURBT.

6.2 REVIEW OF LITERATURE

T1G3 bladder cancer is associated with an aggressive course among superficial bladder tumors. They have a high propensity to recur and also to upstage to T2 disease. They are associated with a significant risk of metastasis and death. Literature shows long-term death rates as high as 34%.[7] An extremely variable 5-year progression rate ranging from 20 to 75% exists, probably due to the different risk subgroups in this spectrum of T1G3 26. Identifying these subgroups and the associated risk factors will help plan an effective management. The goal of the treatment of T1G3 bladder cancer is to decrease the mortality, ensure reduced morbidity and achieve a good quality of life. The dilemma facing the urologist is how best to treat these tumors in a timely manner so that the chances of bladder preservation and cancer control are maximized, while the risks of overtreatment with radical therapy are minimized.[8]

To assess the role of conservative management in pT1G3 bladder cancer,

a number of issues need to be considered:

- Is it really a pT1G3 tumor?
- The variability of pT1G3 bladder cancer
- The quality of clinical data

To confirm the stage and grade as pT1G3

The management protocol for patients with different stages of the disease (pTa, pT1 and pT2 or greater tumors) varies substantially.[9] Pathologists hold a key position in making a diagnosis and in commenting on the accurate stage & grade of a patient's tumor. They must be presented with suitable material along with relevant clinical information: the case is then best reviewed in the setting of a multidisciplinary uro-oncology meeting.[10] The pathologist must receive muscle bearing specimens to determine whether muscle invasion has occurred. In 40% of 58 patients with apparently pT1 disease reviewed by Herr, muscle had not been included in the resection specimens from

the referring hospital.[11] The uniformity of the pathologist's report, assuming adequate specimens, also needs to be accounted for. Evidence suggests that not only do experienced uropathologists vary in their diagnoses, they also may be inconsistent regarding the same specimen.[12] Results in one study revealed that general pathologists tend to overstage tumors, but undergrade them.[13] A close liaison between the urologist and the pathologist, preferably in a multidisciplinary team meeting is hence important.

The variability of pT1G3 bladder cancer

Data on the untreated natural history of pT1G3 tumors is sparse, as these tumors generally require more than just a TURBT.[14-15] Heney and colleagues reported a progression rate of 48% at around 3 years in 27 patients with pT1G3 tumors.[16] This, however, was before the widespread use of intravesical treatments such as BCG. They were considered as tumors with high potential to invade the muscle.It was noticed that the risk of progression and death from disease for patients with pT1G3 tumors is up to 10-fold greater than that for patients with other pTa and pT1 tumors . As long-term data on the use of intravesical Bacillus Calmette-Gue´rin (BCG) has become available over the last twenty years, the idea of the so-called "rule of threes" has emerged, viz., of all the patients treated with BCG, approximately one third survive with their bladder intact, around a third require radical cystectomy, and around a third die of their disease.[17] This difference in outcome varies markedly from the very low progression rates seen with pTa tumors , to the relentlessly aggressive course of muscle-invasive disease. The dilemma, therefore, is to treat adequately, but not to over-treat. The outcome for patients with pT1G3 tumors also seems to be strongly influenced by the presence or absence of carcinoma in situ (CIS).[18] The presence of associated CIS must therefore be carefully considered in the case for conservative treatment of a patient with a pT1G3 tumor.

The quality of clinical data

Patients may present with primary or recurrent tumors, with and without CIS, and with or without other factors that may influence the outcome, such as the presence of tumor in the prostatic urethra or the upper tracts.[19] Even with the information obtained from the systematic reviews and meta-analyses, at present, the "best" way to manage patients with pT1G3 bladder cancer is not clear.

TREATMENT OPTIONS IN T1G3 BLADDER CANCER:

Transurethral Resection of Bladder Tumor

Transurethral resection of the bladder tumor (TURBT) is the first step in the initial treatment of bladder cancer. A TURBT is both diagnostic and therapeutic, and the procedure provides critical staging information. In the setting of a TURBT, the configuration (flat, sessile, or papillary), location (trigone, base, dome, or lateral walls), size (centimeters), and number of tumors should be noted. Tumors have to be completely resected and muscularis propria must be included in the specimen to ensure adequate resection, thorough histological evaluation, and accurate clinical staging.

Larger tumours must be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. The specimens from different fractions have to be referred to the pathologist in separate containers. Cauterization has to be avoided as much as possible during the resection to prevent tissue destruction. The pathologic report should specify the grade of the lesion & the depth of tumour invasion into the bladder wall. It must also and give information on whether the lamina propria and muscle are present in the specimen. A complete and correct TUR is essential for the prognosis of the patient.

Role of random biopsies

In the 1970s, the bladder cancer was believed to be a multifocal tumor with co-existing CIS distant from the primary tumour.[19] Biopsies from the normal looking mucosa were also recommended.[20] The role of random biopsies was questioned and in the recently published EAU guidelines: It is not routinely recommended.

Fujimoto *et al.*[21] and Van der Meijden *et al*[22] assessed the usefulness of random bladder biopsies of normal bladder mucosa after TURBT. Cancer was identified in only few biopsies and was thought to be un-warranted. If needed, multiple random biopsies were needed only in patients with multiple papillary tumors or in those with positive cytology results.

Conversely, May *et al*[23] found that random bladder biopsies altered therapy in 7% of 1033 consecutive patients. In fact, in 14 patients, malignancy was identified in only the random biopsies and not in the resection of the primary tumor. Importantly, however, these investigators excluded patients with small, primary, solitary bladder tumors. It was concluded that the patients with low- risk–appearing tumors and negative cytology results need not undergo random biopsy.

Role of Immediate Adjuvant Intravesical Chemotherapy

Clear consensus exists on the role of prophylactic chemotherapy in the first 6 hours after TUR. In an effort to reduce this risk, many trials have investigated the use of prophylactic or adjuvant intravesical therapy at the time of TURBT. Tolley *et al*[24] performed a multicenter, randomized trial of 502 patients with either Ta or T1 urothelial carcinoma. Those who received intravesical mitomycin C (MMC) within 24 hours of TURBT had a statistically significant decreased risk of tumor recurrence versus those who received placebo. Sylvester *et al.*[25] performed a meta-analysis on this and concluded that adjuvant

intravesical therapy is the treatment of choice in patients with a single, low-grade superficial bladder tumor and should be the initial treatment (before subsequent intravesical BCG) in those with higher-risk bladder tumors. Multicenter, randomized, prospective studies demonstrate that the risk of recurrence can be reduced by half at 2 years and by 15% at 5 years with a single dose of adjuvant intravesical chemotherapy 54. Routine use of prophylactic chemotherapy after TUR can thus be recommended. Contraindications to its use include very deep resections, bladder perforation, and prior documented allergic reaction. Although a wide variety of chemotherapeutic agents were used in the pooled trials (mitomycin C [MMC], doxorubicin, epirubicin, and thiotepa), the majority of centres use MMC (40 mg in 40 cc of saline) as the prophylactic chemotherapeutic agent of choice.

A Second TURBT

T1G3 TCC of the bladder is associated with a significant risk of tumor progression and recurrence when transurethral resection (TUR) is the only treatment. Adjuvant immediate post TUR intravesical chemotherapy or maintenance immunotherapy can reduce this risk; however, long-term results of more than 15 years of follow-up indicate that almost 50% of the patients may end up in a radical surgery for the disease, or even die due to the cancer. The alternative to TUR is cystectomy at either the initial presentation or time of first recurrence. Although the results of this treatment strategy are encouraging, an unknown percentage of patients will lose their bladder and go on to experience all possible complications of urinary diversion unnecessarily- this option does seem to be overkill.

The concern of conservative treatment lies in the quality of TUR. With the available literature it is evident that a 'perfect TUR' cannot be performed on every patient, i.e. macroscopical clearance of the tumor from the bladder, separate resection of the tumor base, inclusion of the deep muscle in the specimen and separate biopsies of the borders of

the resection area. Even in cases of a so-called 'correct TUR', a significant proportion of residual tumors is left behind and will be the source of local recurrence or progression.

6.3 AIMS AND OBJECTIVES OF THE STUDY

The primary aim of this study is to assess the clinical value of reTURBT in patients stratified by clinical indi-cations.

The secondary aim of the study is to compare the safety of TURBT and reTURBT.

7.0 MATERIALS AND METHODS

STUDY DESIGN - The study design is a prospective observational study.

SAMPLE SIZE – Time bound study

7.1 SOURCE OF DATA:

The study will be conducted among the patients admitted to department of Urology, Dayanand Medical College and Hospital, Ludhiana from 21st November, 2022 to 1st February 2024.

7.2 METHOD OF COLLECTION OF DATA

Information shall be collected through a pre- designed performa for each patient chosen to be a part of the study with detailed history, clinical examination and complete investigational workup. Details of the study explained to each case. Analysis will be done with the collected details prospectively. A pre-informed consent from each patient shall be taken.

During initial cystoscopy, the operative details such as the number of lesions, solid or papillary configuration of lesions and the site of lesions will mapped and recorded. After complete TURBT, a deep biopsy from the base of the tumor will be taken. The TURBT chips and the deep biopsy will be sent separately. Restage TURBT is advised at 4–6 weeks from initial TURBT as per the EAU guidelines. The cystoscopic findings will be recorded during the restage TURBT similar to that at the initial TURBT. In patients with no obvious tumors, resection of the tumor bed will performed and sent for analysis. Post restage, the patients will be then managed by a standard treatment protocol and follow-up. The complications of restage TURBT and recurrences and progression will recorded in the follow-up.

INCLUSION CRITERIA

1. Patients with T1 high grade bladder cancer
2. Patents with age >18 years

EXCLUSION CRITERIA:

1. Multiple comorbidities
2. Patient with uncorrected coagulopathy

DURATION OF STUDY – 21st November, 2022 to 1st February, 2024.

OUTCOME: The outcome of this study will be determine by number of cases undergoing reTURBT having recurrence, upstaging of tumor or no growth in final histopathology report.

STATISTICAL ANALYSIS

Data will be described in terms of range, mean +/- , standard deviation, frequencies (number of cases) and relative frequencies (percentages) For discrete data -proportion is computed and the mean and standard deviation will be computed for the continuous data. The chi square test will be applied to compare the proportions between the groups to assess the statistical significance. All analyses will be two tailed and p <0.05 will be considered significant. SPSS version 21.0 will be used for data analysis.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS ORINTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

Routine, Renal Ultrasound , CECT – KUB ,

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached here with.

PROFORMA

Name:

Age:

Chief Complaints: X months **Sex:** M / F

O / E:

Creatinine: mg%.
Cytology:

Radiology: USG:

IVU:

CECT:

Radiology Staging:

Past History: smoking yes/no

Procedure Details
Date:

No. of lesions: single/ Multiple

Size:<3 cm / > 3 cm

SIGNATURE OF CANDIDATE

SIGNATURE OF SUPERVISOR

Site:

Bladder neck / Dome

Posterior wall / Anterior wall

Left lat wall / Right lat wall

Assosiated lesions:

Appearance: Invasive / Non invasive Bimanually

Complications:

Biopsy: CIS / Ta / T1 / T2 / T3 / T4

PUNLMP / Low Grade / High Grade

G1 / G2 / G3

Muscle in specimen:

Re TURBT for STAGING

Procedure: Re TURT (for staging)
Date:

SIGNATURE OF CANDIDATE

SIGNATURE OF SUPERVISOR

Previous scars: Recurrence: Y / N

No. of lesions: single / Multiple

Size:<3 cm / > 3 cm

Site:

Bladder neck / Dome

Posterior wall / Anterior wall

Left lat wall / Right lat wall

Re resection from:

Distance from orifice:

Associated lesions:

Appearance: Invasive / Non invasive

Complications:

Biopsy: No tumor Same stage/grade

Up stage

Down stage

Previous: CIS / Ta / T1 / T2 / T3 / T4

PUNLMP / Low Grde /HIgh Grde

Now : : CIS / Ta / T1 / T2 / T3 / T4

PUNLMP / Low Grde /High Grde

SIGNATURE OF CANDIDATE

SIGNATURE OF SUPERVISOR

CERTIFICATE OF DEPARTMENTAL CLEARANCE

This is to certify that the plan of thesis entitled **"TO DETERMINE THE ROLE OF RE-RESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER"** has been discussed in the Department of Urology and approved by whole of the faculty of the department. The plan writing is satisfactory.

Supervisor

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DAYANAND MEDICAL COLLEGE & HOSPITAL

LUDHIANA

Ref. No: DMCH/

Dated :

TO WHOM IT MAY CONCERN

Certified that the study entitled **"TO DETERMINE THE ROLE OF RE-RESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER"** involves only such investigations and / or treatment, which are relevant in the management of patients and has no extra cost implications to the patient.

Name of candidate: Dr. Nikhil Chauhan

Supervisor: Dr. Arvind Goyal

Co-Supervisor: Dr. Harmandeep Singh Chahal

Dr. Aminder Singh

Signature of candidate

Signature of Supervisor

DAYANAND MEDICAL COLLEGE & HOSPITAL,
LUDHIANA

Ref. No. DMCH/ Dated:

TO WHOM IT MAY CONCERN

I shall carry out the study **"TO DETERMINE THE ROLE OF RE-RESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER"** meticulously and shall maintain the records for 5 years after the submission of thesis and present them to any competent authority as and when required. The following documents will be preserved:

1. List of enrolled patients with identification details
2. Consent forms of all the enrolled patients
3. Proforma of each patient with verifiable details, individually signed by supervisor.

Dr. Nikhil Chauhan
MCh Resident
Dept. of Urology
DMC& Hospital, Ludhiana

CERTIFICATE

We hereby certify that the informed patient consent form and its translation and back translation to Hindi and Punjabi are accurate to the best of our knowledge and satisfaction.

Supervisor

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INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....
.....am willing to participate in the study **"TO DETERMINE THE ROLE OF RE-RESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

.....
Signature of the patient

Name:

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"TO DETERMINE THE ROLE OF RE-RESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

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गवाह के हस्ताक्षर

नाम:

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रोगी के हस्ताक्षर/अंगूठे का निशान

नाम:

_____

अन्वेषक केहस्ताक्षर

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विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"TO DETERMINE THE ROLE OF RE-RESECTION IN HIGH GRADE NON-INVASIVE BLADDER CANCER" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ। ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

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ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ